A STUDY TOWARDS THE SYNTHESIS OF 3,4,7,8-TETRAHYDROAZOCINE AND ITS DERIVATIVES

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ABSTRACT

Attempted syntheses of 3,4,7,8-tetrahydroazocine 2a, 4-bromo-3,4,7,8-tetrahydroazocine 2b and 4-methoxy-3,4,7,8-tetrahydroazocine 2c have been performed via the heterolytic fragmentation of their corresponding precursors such as 4-endo-p-toluenesulfonyloxy-octahydrocyclopenta[b]pyrrole 28, 4-exo-5-endo-dibromo-octahydrocyclopenta[b]pyrrole 29 and 4-exo-bromo-5-endo-methoxy-octahydrocyclopenta[b]pyrrole 30, respectively.

The preparation of 4-endo-p-toluenesulfonyloxy-octahydrocyclopenta[b]pyrrole 28 was achieved starting from cyclopentenone 44 in five steps. Photochemical cycloaddition of cyclopentenone with 1,1-diethoxyethene gave cis-6,6-diethoxybicyclo[3.2.0]-heptan-6-one 31, which upon lithium aluminium hydride reduction and acid hydrolysis gave 2-hydroxy-bicyclo[3.2.0]-heptan-6-one 32. Reaction of 32 with the highly reactive O-mesitylenesulfonylhydroxylamine (MSH) 70 afforded 4-hydroxy-2-oxo-octahydrocyclopenta[b]pyrrole 33a in excellent yield. Treatment of 33a with sodium hydride and then with p-toluenesulfonyl chloride gave 4-endo-p-toluenesulfonyloxy-2-oxo-octahydrocyclopenta[b]pyrrole 35 which was reduced by

diborane to yield the desired compound 28.

Similarly, 4-exo-5-endo-dibromo-octahydrocyclopenta[b]pyrrole 29 and 4-exo-bromo-5-endo-methoxy-octahydrocyclopenta[b]pyrrole 30 were also prepared starting from cyclopentadiene in five steps.

Thermal cycloaddition of cyclopentadiene with dichloroketene gave 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one 36, which upon treatment with MSH, gave exclusively 3,3-dichloro-2-oxo-hexahydrocyclopenta-4-en[b]pyrrole 42. Dechlorination of 42 was effected in the presence of zinc and acetic acid to give 2-oxo-hexahydrocyclopenta-4-en[b]pyrrole 43. Bromination of 43 in dichloromethane and in methanol afforded 4-exo-5-endo-dibromo-2-oxo-octahydrocyclopenta[b]pyrrole 40a and 4-exo-bromo-5-endo-methoxy-2-oxo-octahydrocyclopenta[b]pyrrole 41a, respectively. Diborane reduction of 40a and 41a gave the desired 29 and 30 respectively.

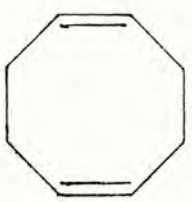
No fruitful result was obtained on the solvolytic reactions of 28, 29 and 30 in ethanolic solution. However,

solvolytic studies of 29 and 30 in tetrahydrofuran gave promising results as shown by their GC-MS. Further work is required to establish this preliminary observation.

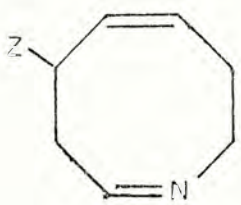
LIST OF TABLES

INTRODUCTION

Considerable attention has been directed to the study of 1,5-cyclooctadiene (COD) (1), particularly as an organic substrate in many organometallic reactions.[1] Because this monocyclic hydrocarbon (C_8H_{12}) is known to undergo various unusual reactions, it has, therefore, been a prime target for many interesting mechanistic and synthetic studies. Not surprisingly, intense interest in 1 still persists to the present day.



1



2 a, Z=H
b, Z=Br
c, Z=OCH_3

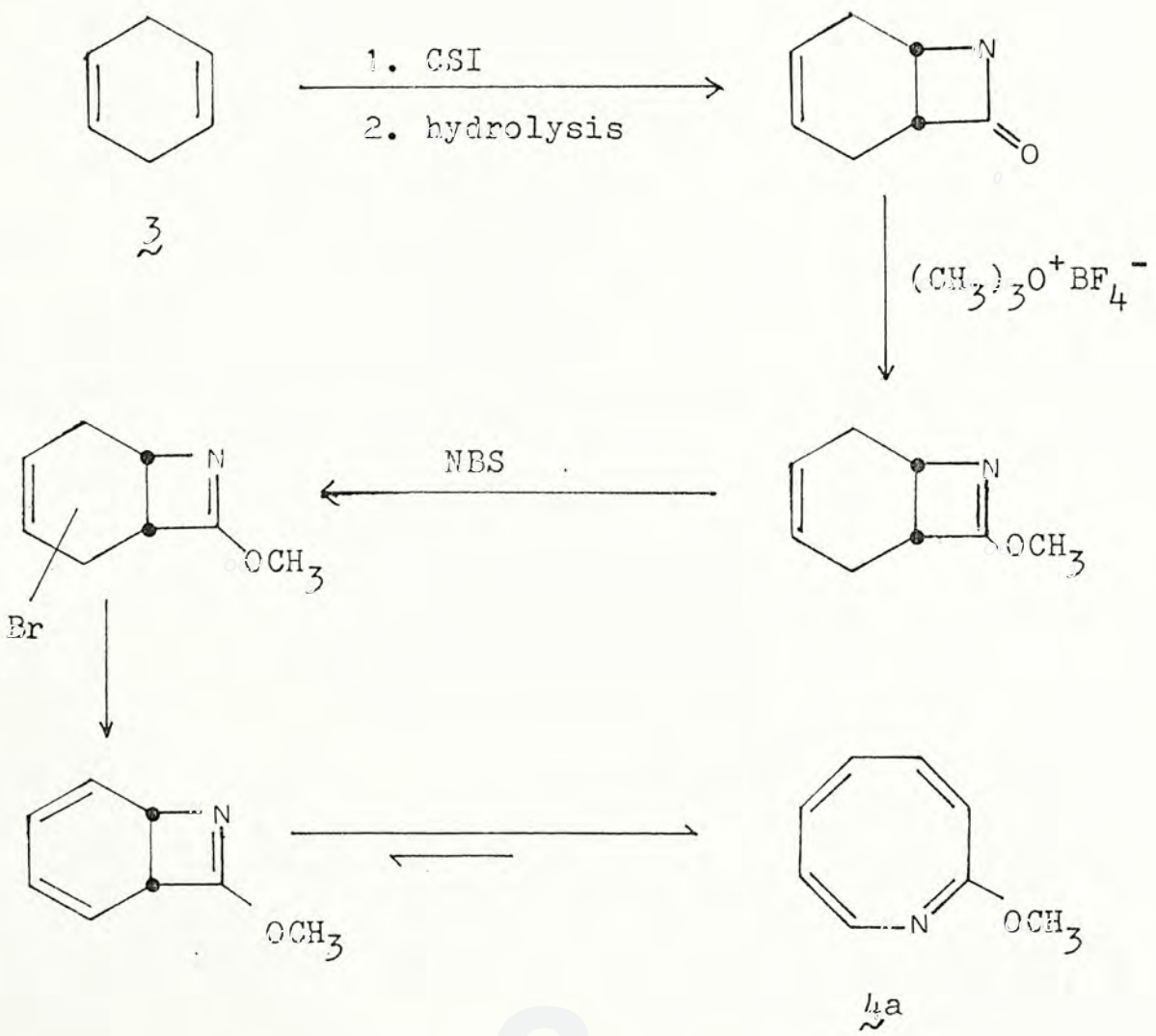
Despite of the marked progress in the study of COD, no eight-membered monoheterocyclic analogs of 1 has been described. This particular investigation began with two aims — first, the development of a general synthesis of 3,4,7,8-tetrahydroazocine (2a) and its 4-substituted

derivatives, e.g. (2b) and (2c), and second, elucidation of the unconventional structural and chemical properties almost certainly to be associated with such monocyclic π-equivalent congeners of 1. In continuation of the interest in 3,4,-7,8-tetrahydroazocine chemistry,[2] this thesis describes the study on a convenient entry to this class of heterocycles.

LITERATURE SURVEY

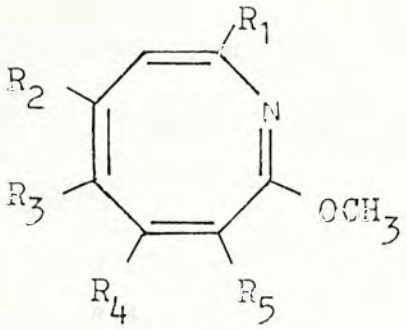
The first monocyclic π-equivalent heterocyclic congeners of cyclooctatetraene, 2-methoxyazocine (4a), was synthesized by L.A. Paquette et. al. from 1,4-cyclohexadiene (3) (Scheme I).[3,4] This general synthetic route also led to the preparation of several methylated derivatives of 4a, 4b-4e, from the corresponding methylated derivatives of 3.

Scheme I



3

4a



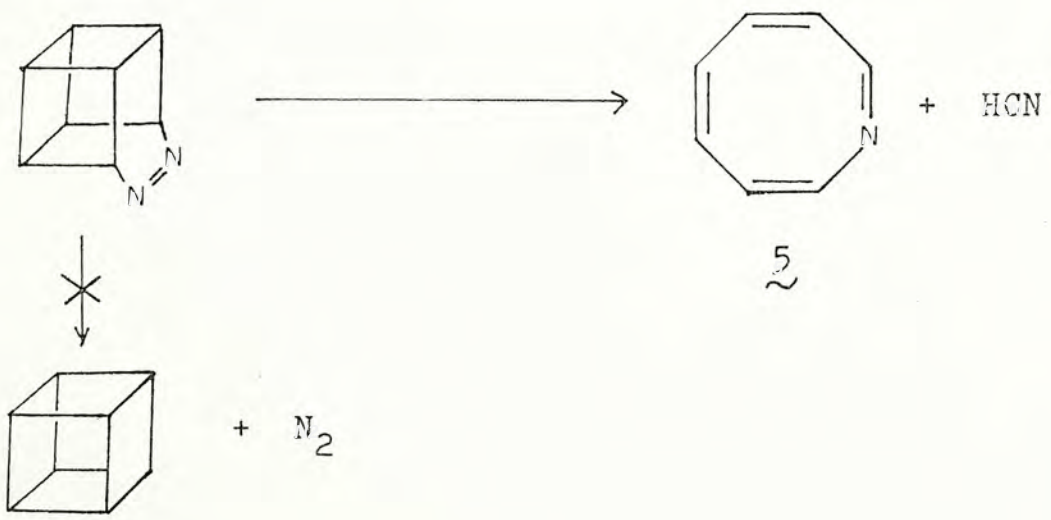
4 b, $R_1=CH_3$, $R_2=R_3=R_4=R_5=H$

c, $R_1=R_5=CH_3$, $R_2=R_3=R_4=H$

d, $R_1=R_2=R_4=CH_3$, $R_3=R_5=H$

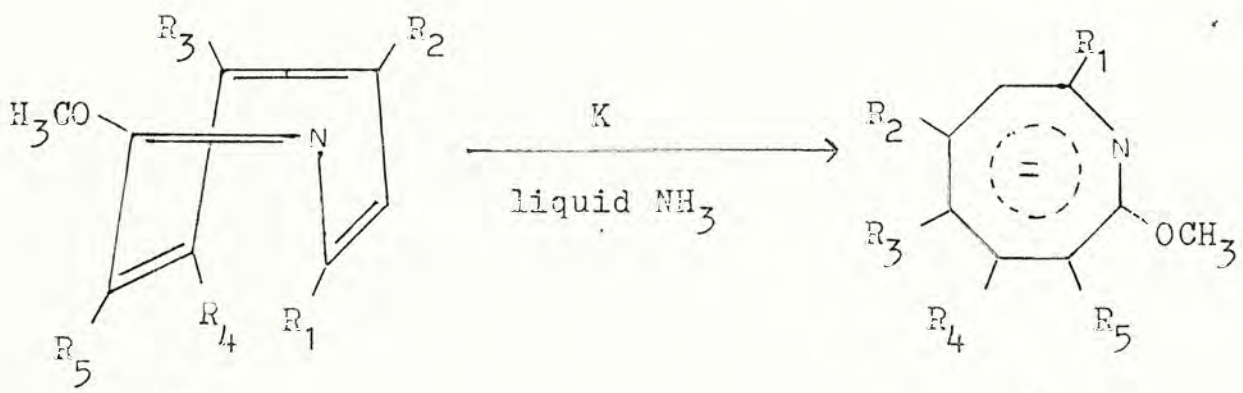
e, $R_1=R_2=R_3=R_5=CH_3$, $R_4=H$

The parent compound, azocine (5), was however synthesized accidentally.[5] Instead of ring closure to cubane which was the purpose of the experiment, flash vacuum pyrolysis of diazabasketene underwent a novel fragmentation to give 5 and hydrocyanic acid.



Unlike 2-methoxyazocine and its methylated derivatives which are stable compounds, the azocine molecule is a highly reactive, acid-sensitive species and readily decomposes upon warming <u>in vacuo</u> to temperature above -50°C.

Similar to the cyclooctatetraene,[6] the four double bonds in the 2-methoxyazocine compounds 4a-4e were found to lack appreciable conjugative interaction due to the preferred "tub" conformation of these heterocycles.[4] However, when they were treated with potassium metal in tetrahydrofuran, dimethoxyethane, or liquid ammonia, they would readily undergo a two-electron reduction to give the planar dianions 6a-6e which have been found to be aromatic.[7] Such azocinyl dianions appeared to be stable and did not undergo skeletal rearrangement.



4 6

a, $R_1=R_2=R_3=R_4=R_5=H$

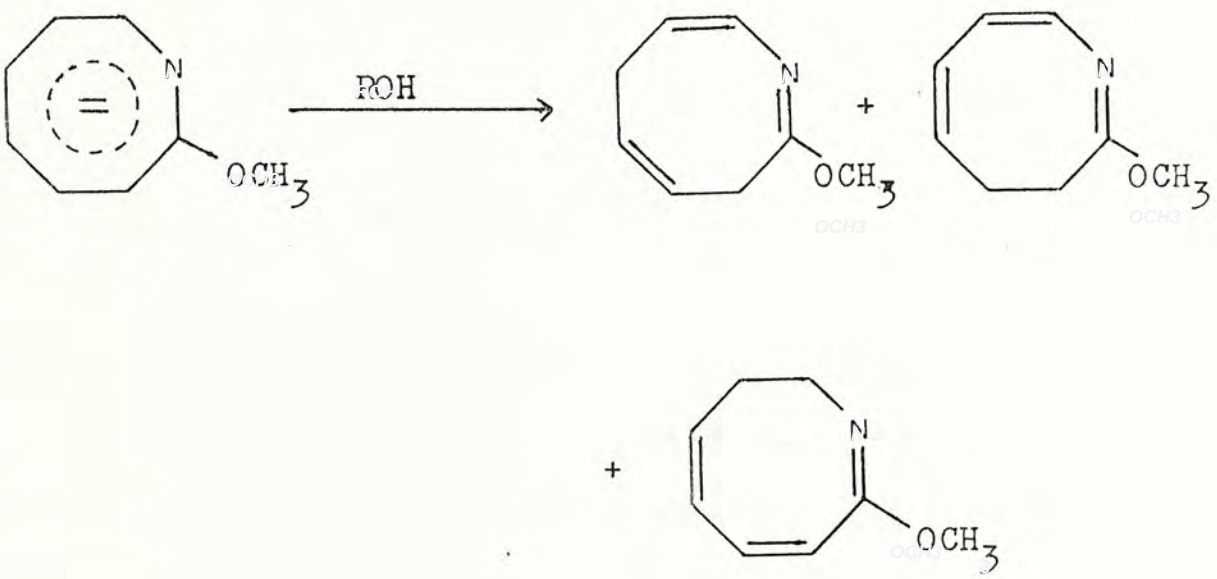
b, $R_1=CH_3$, $R_2=R_3=R_4=R_5=H$

c, $R_1=R_5=CH_3$, $R_2=R_3=R_4=H$

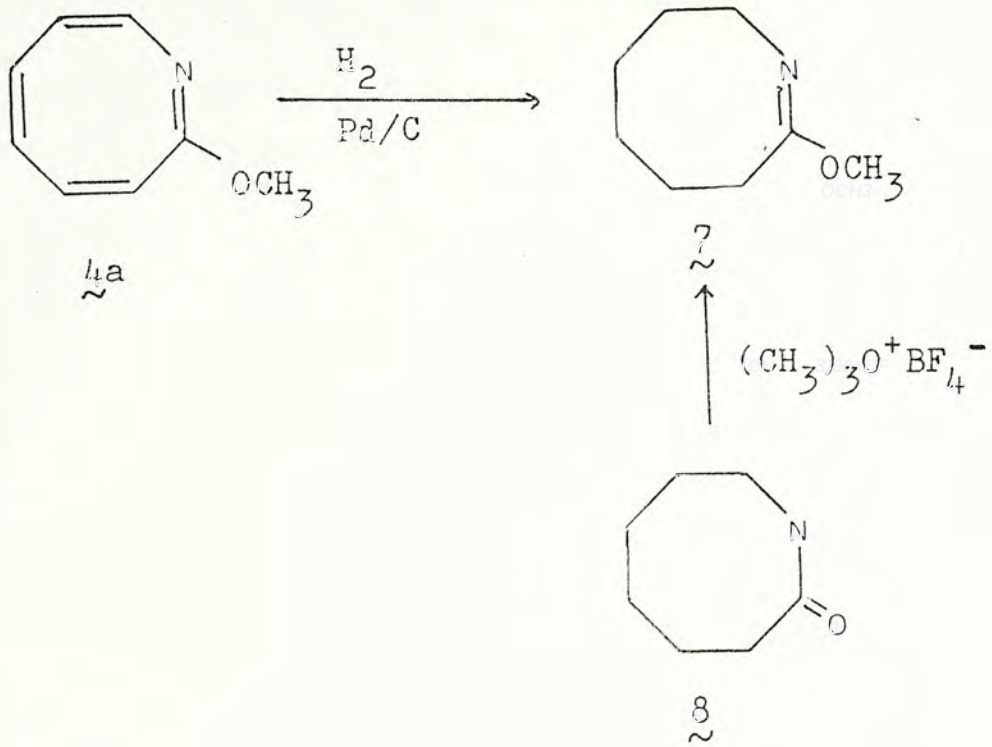
d, $R_1=R_2=R_4=CH_3$, $R_3=R_5=H$

e, $R_1=R_2=R_3=R_5=CH_3$, $R_4=H$

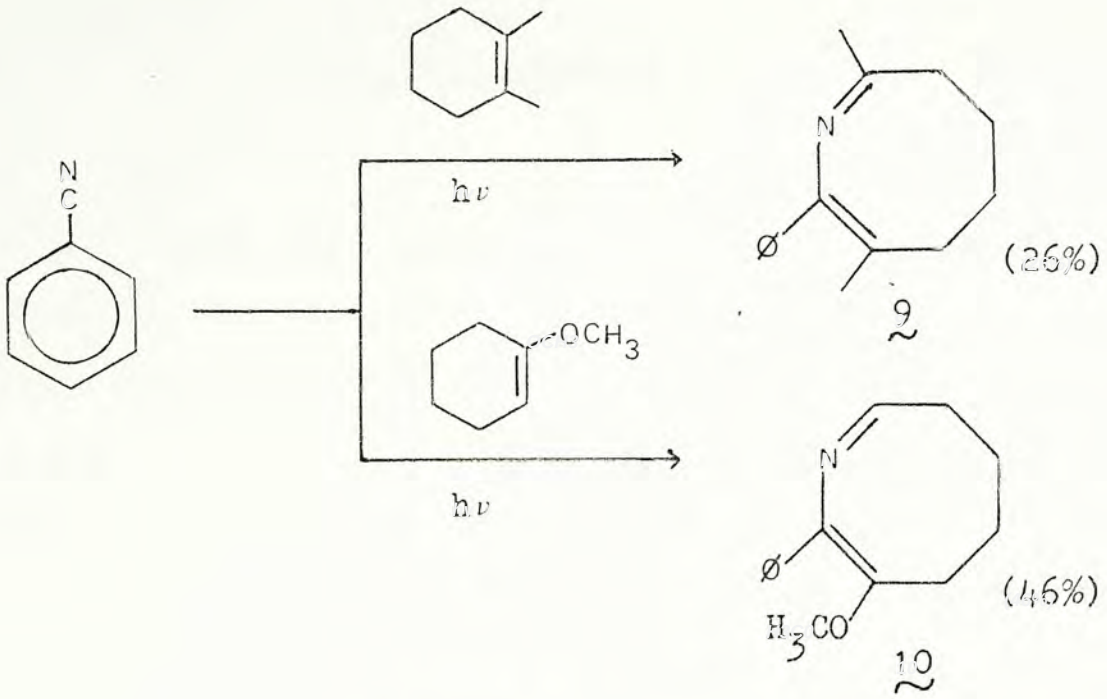
However, protonation of these dianions with various active hydrogen sources (water, methanol, tert-butanol) provided the major synthesis of 3,4- and 3,6-dihydroazocine derivatives, with a little 7,8-dihydro product, in various ratio.[4]



On the other hand, 2-methoxy-3,4,5,6,7,8-hexahydroazocine (7) had been synthesized either by hydrogenation of 4a over 10% palladium on carbon at atmospheric pressure, or reaction of the lactam 8 with trimethyloxonium fluoroborate.[4]



Recently, it has been found[8] that photochemical cycloaddition of benzonitrile to 1,2-dimethylcyclohexene and 1-methoxycyclohexene gave the corresponding 3,4,5,6-tetrahydroazocine derivatives 9 and 10, the products of electrocyclic ring opening of azetines produced by an initial $[_2\pi_s + {}_2\pi_s]$ cycloaddition across the CN function (Scheme II).



Scheme II

Aside from the preparation of the 3,4,5,6-tetrahydroazocine derivatives described above and a few of benzo-fused tetrahydroazocines[9] (Fig I), it is to the best of our knowledge that 3,4,7,8-tetrahydroazocine 2a and its derivatives, e.g. 2b and 2c, have not been reported.

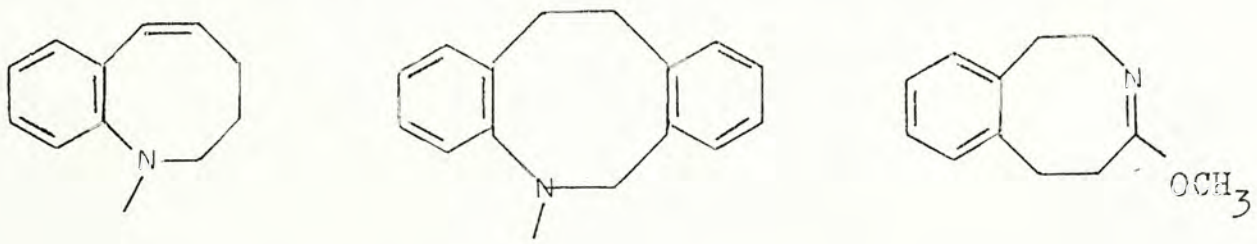
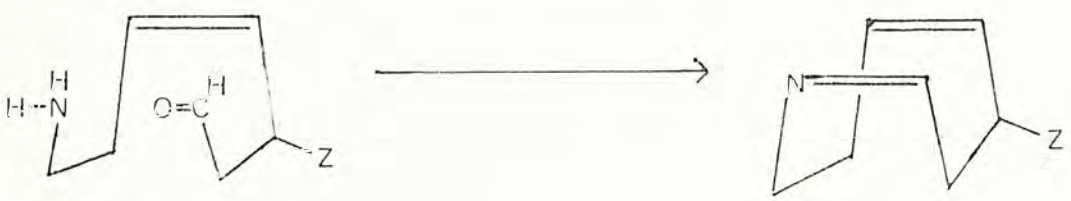


Fig I. Selected benzo-fused tetrahydroazocine derivatives

SYNTHETIC STRATEGY

Since our target compounds 2a-2c contain a cis carbon-carbon double bond and an imine moiety, one obvious route to synthesize these compounds would be a one-step intramolecular cyclization of the corresponding unsaturated α,ω-aminoaldehydes 11a-11c. However, the presence of two reactive functional groups, that is an amino and an aldehyde group, in 11a-11c would make these compounds difficult to be prepared and isolated. Moreover, to our knowledge, no successful intramolecular eight-membered ring imine formation has been reported in the literature.



11 2

a, Z=H
b, Z=Br
c, Z=OCH_3

Heterolytic fragmentation reaction, well studied by Grob and his co-workers[10] in the sixties, appears to be attractive to our present study. It has been shown that

molecules containing certain combination of carbon and heteroatoms, such as O,N,S,P and halogen undergo a regulated cleavage (fragmentation) into three fragments. In the general formulation of equation (i)

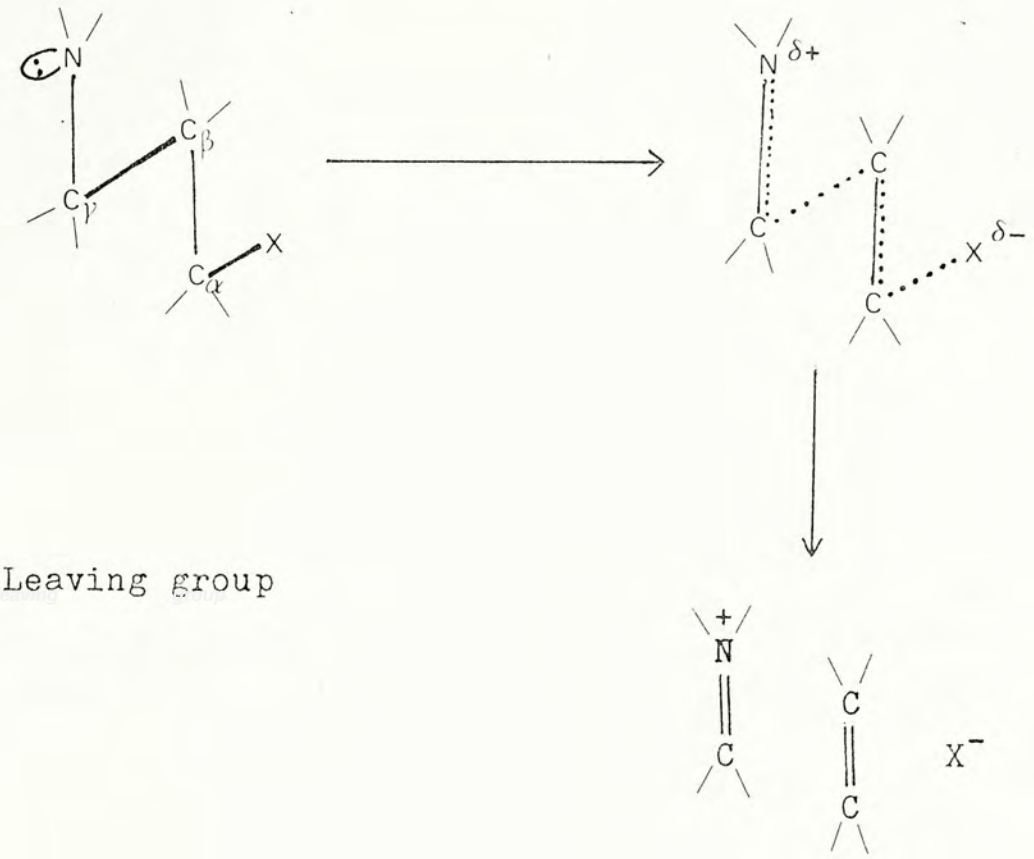
$$a\text{-}b\text{-}c\text{-}d\text{-}X \longrightarrow a\text{-}b + c{=}d + X: \qquad (i)$$

a-b denotes an electrofugal group, which leaves as fragment a-b without the bonding electron pair. The middle group c-d affords the unsaturated fragment c=d, while the nucleofugal group -X leaves in the form of a fragment :X with the bonding electron pair.

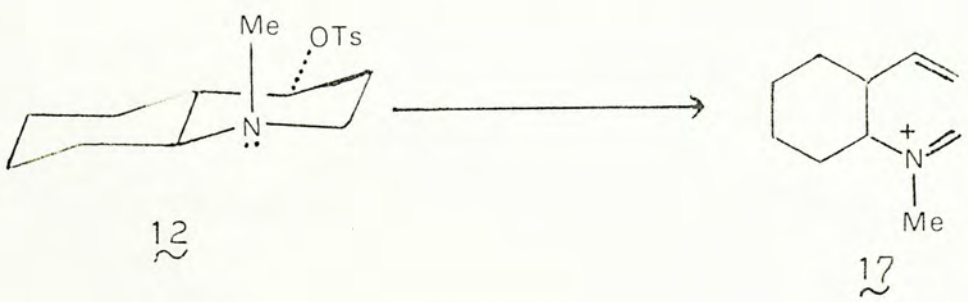
A study of the solvolysis of γ-aminohalides or γ-aminoalcohol derivatives N-C-C-C-X, where X denotes halogen or $-OSO_2R$ as a leaving group, shows that fragmentation may occur by a one-step concerted mechanism or by a stepwise mechanism depending on structural, electronic, and steric factors.[11]

The synchronous or one-step concerted mechanism, which has rigorous structural and stereoelectronic requirements, is operative only if the C_α-X bond and the free electron pair of the nitrogen atom are both orientated anti and parallel

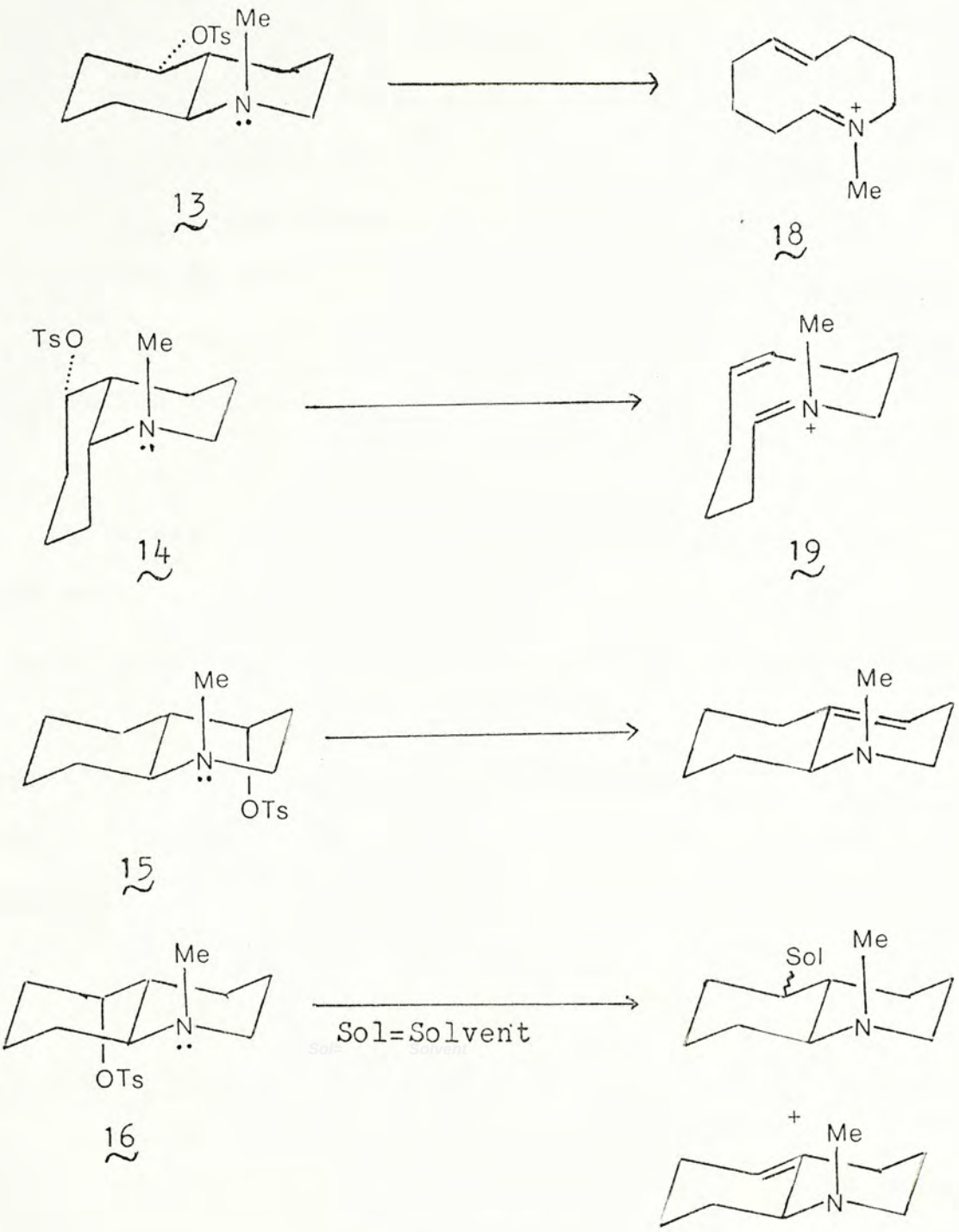
(anti-periplanar) with respect to the C_β-C_γ bond which undergoes cleavage.



There are numerous examples[12] in showing this one-step concerted fragmentation (Scheme III).



12 17

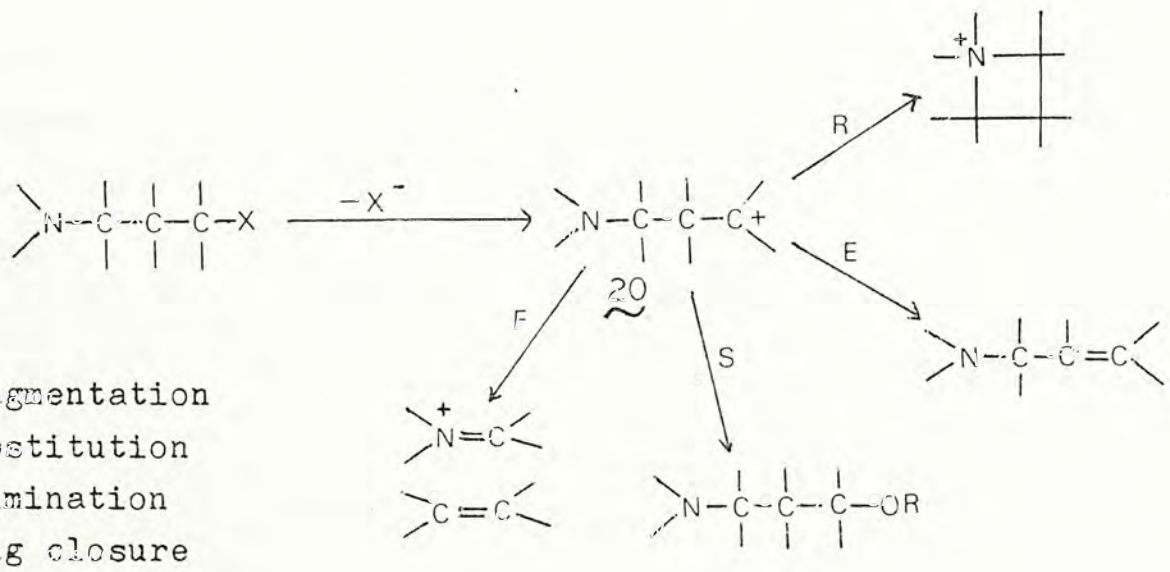


Scheme III

Thus the equatorial tosylates 12, 13, and 14 in which

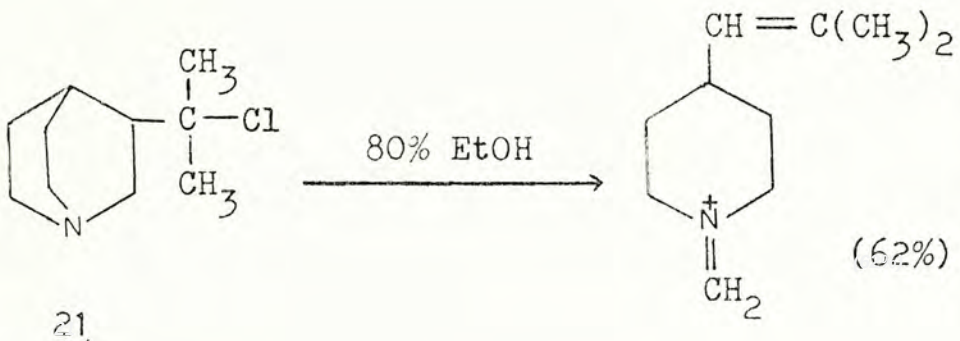
all three electron pairs involved in the synchronous process were able to adopt anti-parallel orientations, afforded exclusively the corresponding fragmentation products 17, 18 and 19. Conversely, the axial tosylates 15 and 16 in which the C_α-OTs bonds were no longer anti and parallel to the C_β-C_γ bond, reacted to yield mainly elimination and substitution products.

The stepwise process began with the loss of the nucleofugal group -X to form a γ-amino carbonium ion 20 as an intermediate. This then broke down in a faster step into an iminium ion and an olefin, thus completing the fragmentation. The cationic intermediate 20 would also react further by substitution, elimination, and ring closure (Scheme IV).



Scheme IV

An example of this stepwise carbonium ion mechanism is illustrated[13] by 3-(chlorodimethyl)-quinuclidine (21), which underwent solvolytic reaction to give 62% of the fragmentation product 22 together with 30% of substitution products and 6% of elimination products.



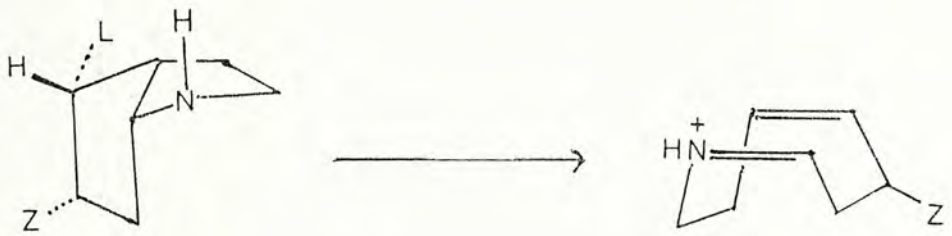
21

22

The present method suggests that a solvolytic fragmentation of a cis-fused octahydrocyclopenta[b]pyrrole with a good leaving group L at C-4 position would lead to the simultaneous formation of C=C and C=N double bonds.

Z=H, Br or OCH_3

On the one hand, when the leaving group L has an endo-configuration, by comparing the structural similarity bewteen 14 and the bicyclic octahydrocyclopenta[b]pyrrole derivatives 23, we should anticipate that 23 would undergo a one-step concerted fragmentation to give the desired eight-membered iminium ion 24.



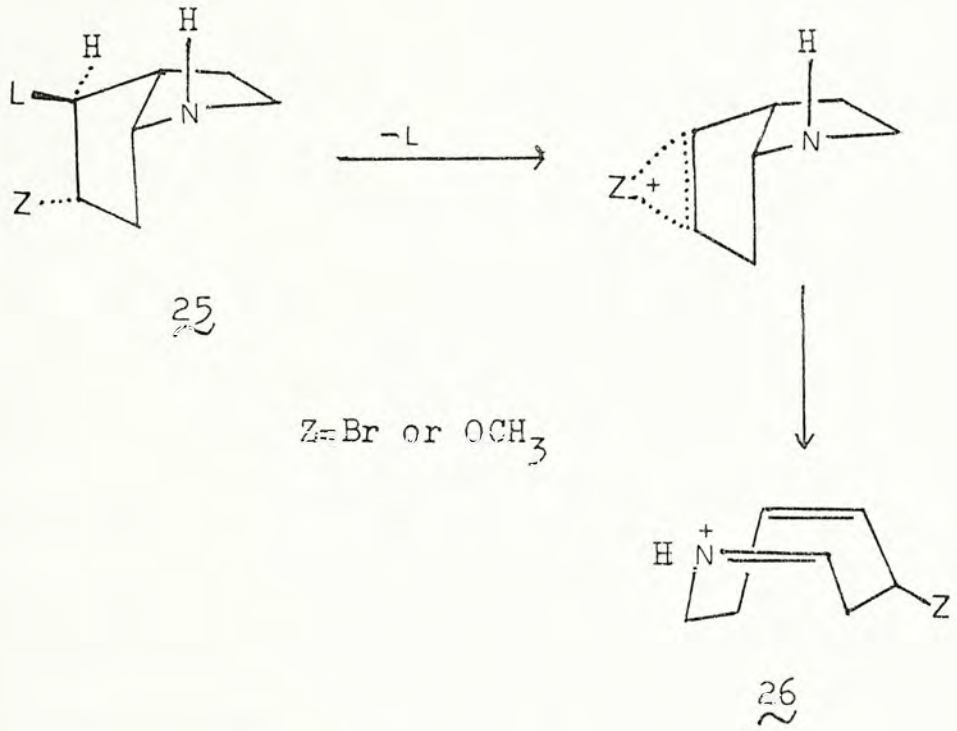
Z=H

23 24

Inspection of the model of 23 revealed that the geometry of the C_α-L bond, the lone pair electrons on the nitrogen, and C_β-C_γ bond are not exactly parallel and anti-periplanar, but the deviation (about 20°) is small and we expect that the concerted fragmentation reaction might occur for compound 23.

On the other hand, when L has an exo-configuration, the bicyclic octahydrocyclopenta[b]pyrrole derivative

25 will not satisfy the parallel and anti-periplanar requirements but it is hoped that 25 would also undergo fragmentation reaction to give the corresponding iminium ion 26 through the stepwise mechanism via the formation of a carbonium ion.



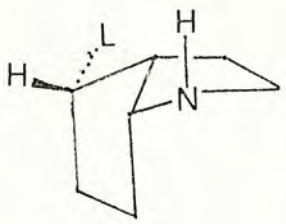
25

Z=Br or OCH_3

26

The main objective of this research project is to synthesize two bicyclic 4-endo substituted amines 27 and 28 which, in the hope that if the one-step concerted solvolytic fragmentation did occur, would give our target compound 2a exclusively. The leaving groups L that had

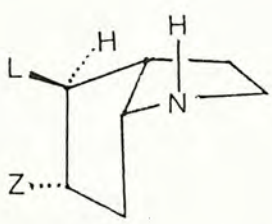
been introduced to the 4-<u>endo</u> position of 23 were methanesulfonate and p-toluenesulfonate groups.



27, L=-OSO_2CH_3

28, L=-OSO_2-C_6H_4-CH_3

However, it is also of an interest to study whether solvolytic fragmentation would occur in the bicyclic 4-<u>exo</u> substituted amines through the stepwise mechanism that would give our target molecules 2b and 2c. So two bicyclic 4-<u>exo</u> substituted amines 29 and 30 had also been synthesized with a bromide as the leaving group.



29, L=Br, Z=Br

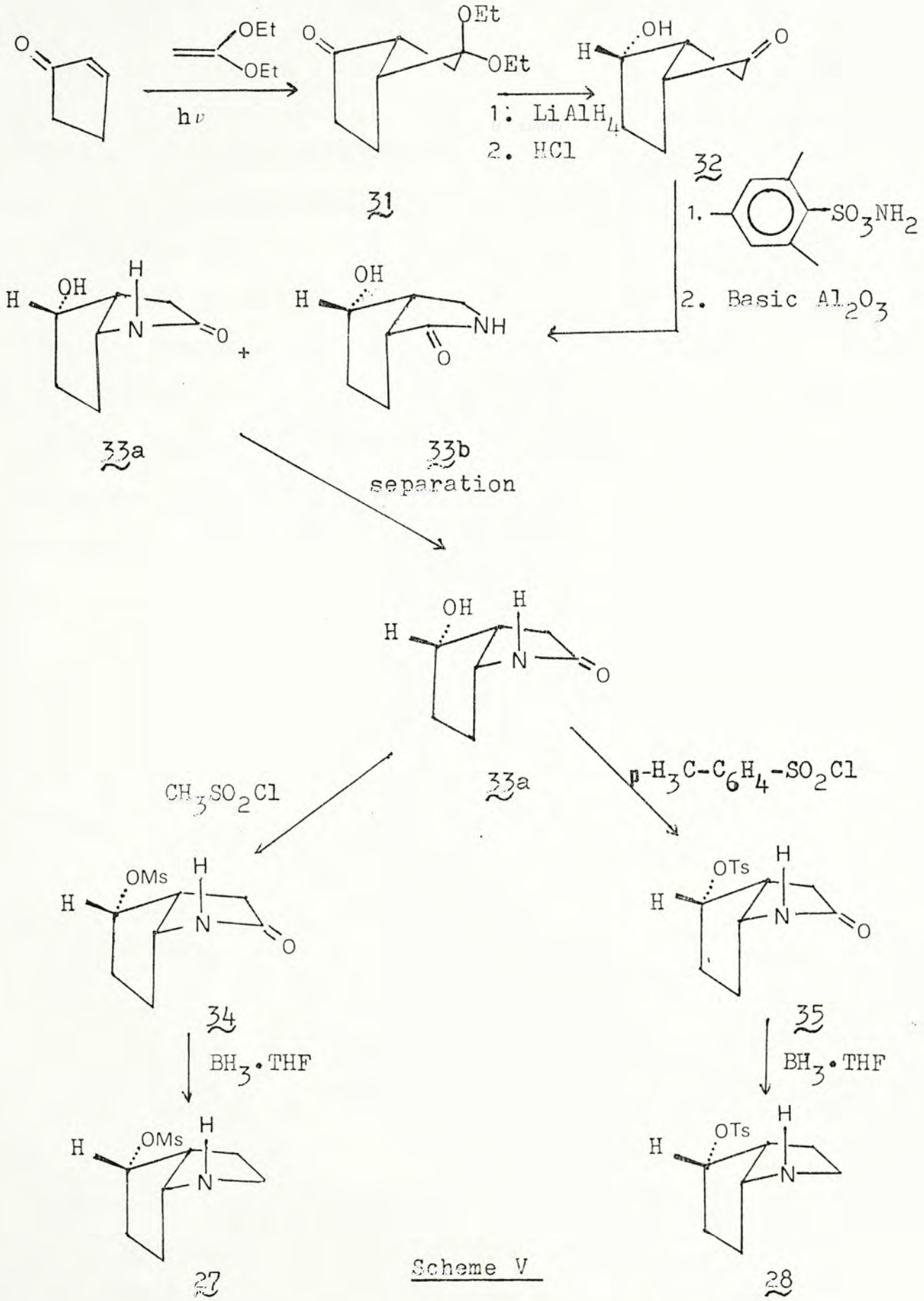
30, L=Br, Z=OCH_3

By far the substrate, γ-aminoalcohol derivatives, which appeared in the literature to proceed fragmentation were exclusively tertiary amines. However, their secondary amine counterparts were apparently not known.

The synthesis of 27, 28, 29 and 30 presents a challenge to us as no satisfactory synthesis of 4- and 4,5- substituted octahydrocyclopenta[b]pyrrole has been reported in the literature. Our synthetic plan focuses on a stereospecific and regiospecific generation of cis-fused azabicyclo[3.3.0]octane skeleton and simultaneous introduction of a good leaving group at the C-4 position with an endo or exo stereochemistry.

Synthesis of 4-endo-methanesulfonyloxy-octahydro-penta[b]pyrrole (27)[14] and 4-endo-p-toluenesulfonyloxy-octahydrocyclopenta[b]pyrrole (28)

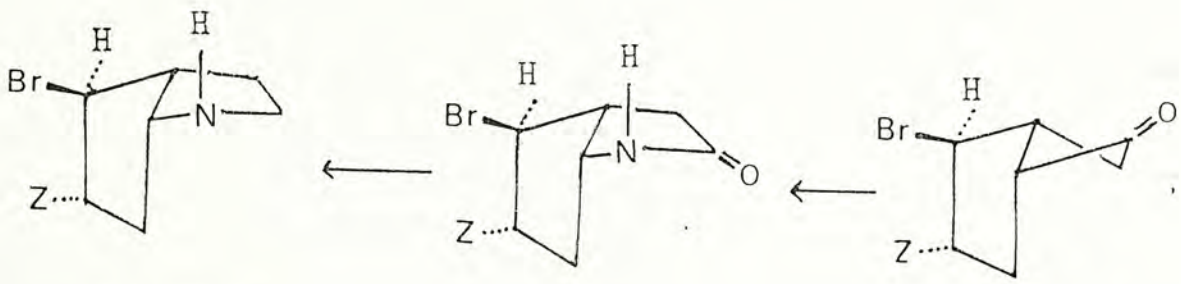
Adapting the synthetic pathway that was proposed by Chow,[2] compounds 27 and 28 could be synthesized from readily available starting materials as outlined below (Scheme V).



Scheme V

Synthesis of 4-exo-5-endo-dibromooctahydrocyclopenta[b] pyrrole (29) and 4-exo-bromo-5-endo-methoxyoctahydrocyclo-penta[b]pyrrole (30)

Similar to 27 and 28, the azabicyclo[3.3.0] skeleton of the 4-exo-5-endo substituted octahydropenta[b]pyrrole system could be synthesised by a Beckmann type rearrangement of a bicyclo[3.2.0] derivatives 38 and 39. The bicyclic amines 29 and 30 were then produced by the borane reduction of the corresponding lactams (Scheme VI).



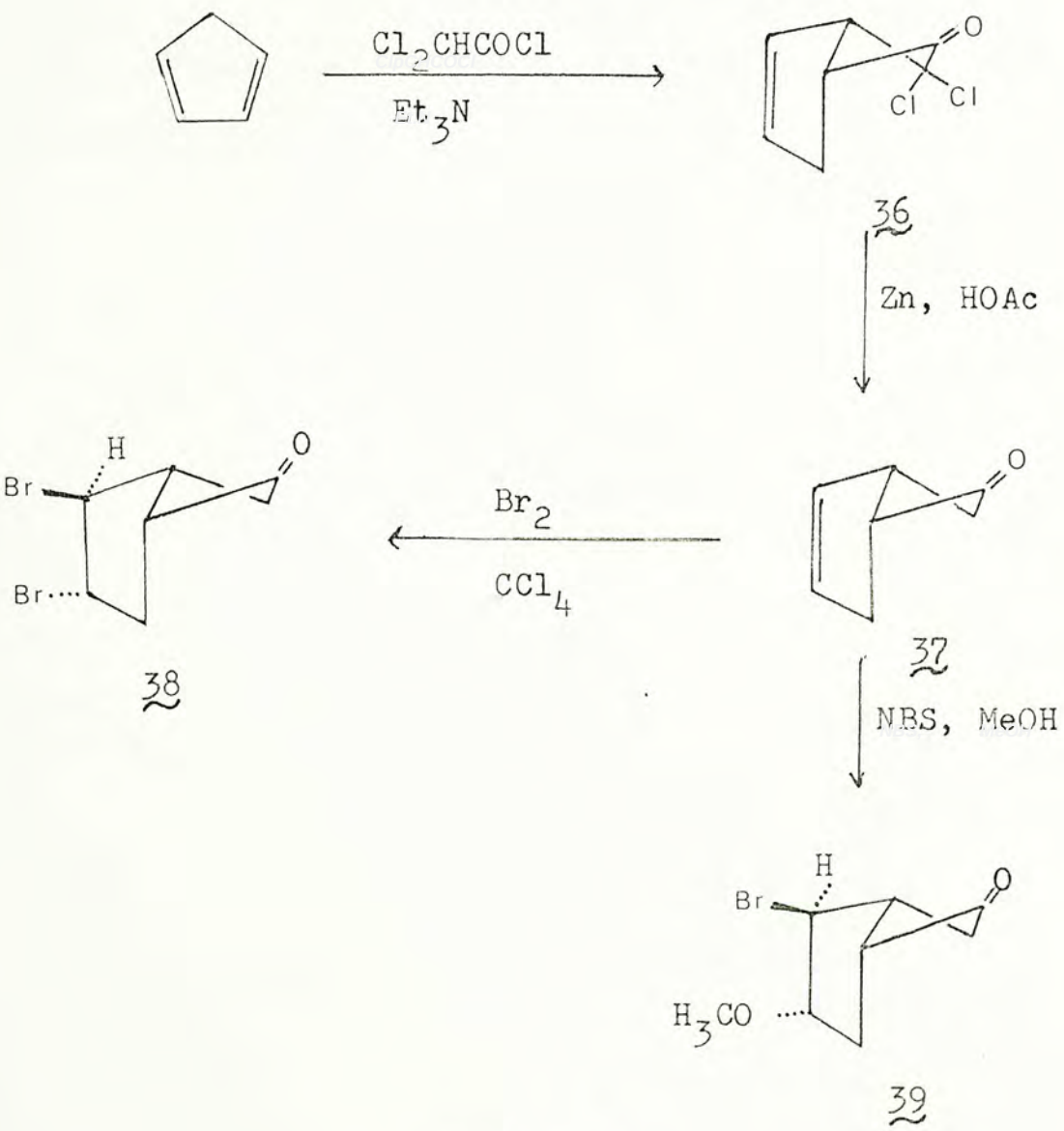
29, Z=Br
30, Z=OCH_3

38, Z=Br
39, Z=OCH_3

Scheme VI

Compounds 38 and 39 could be synthesized from the bromination of bicyclo[3.2.0]hept-2-en-6-one (37) in carbon tetrachloride and in methanol, respectively.[15] Dehalogenation

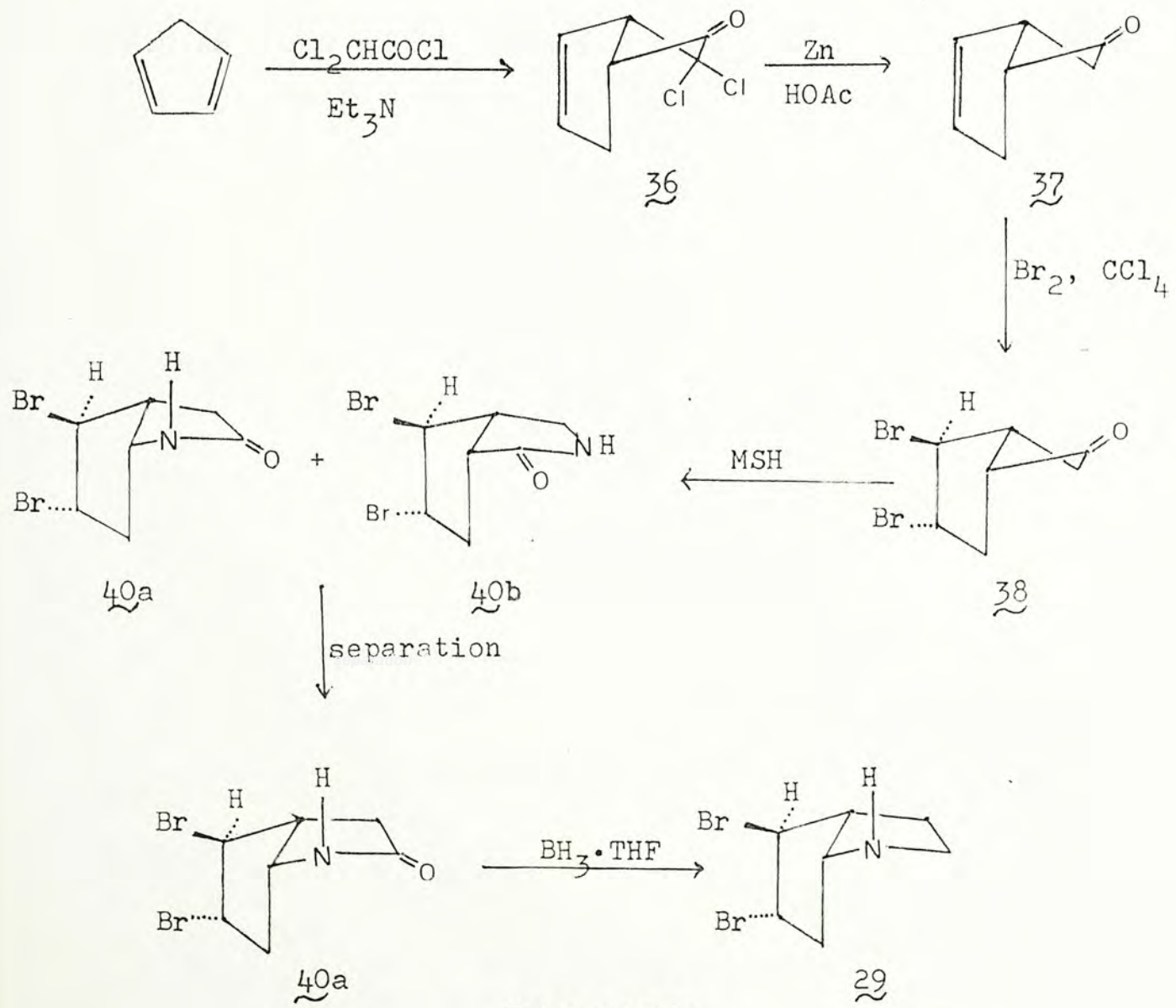
of 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one (36) in the presence of zinc and glacial acetic acid afforded 37 smoothly.[16] Compound 36 could be prepared from a stereoelectronic control of $[_2\pi_s + _2\pi_s]$ cycloaddition of cyclopentadiene and dichloroketene[16] (Scheme VII).



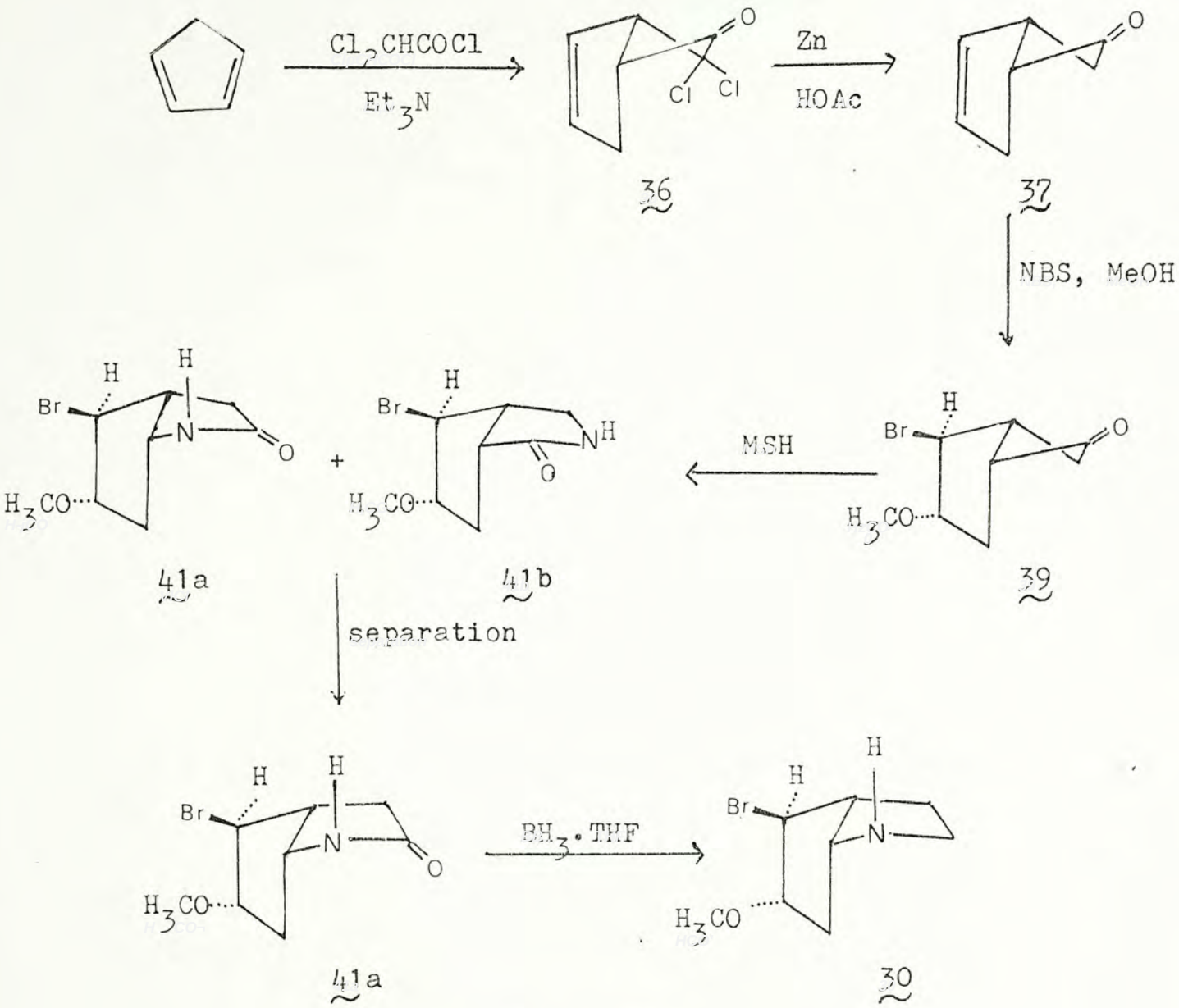
Scheme VII

Bromination of 37 should preferentially attack the less hindered exo site to give the corresponding bromo derivatives 38 and 39 with the desired stereochemistry.

The synthetic plans for compounds 29 and 30 are summarized in Schemes VIII and IX.



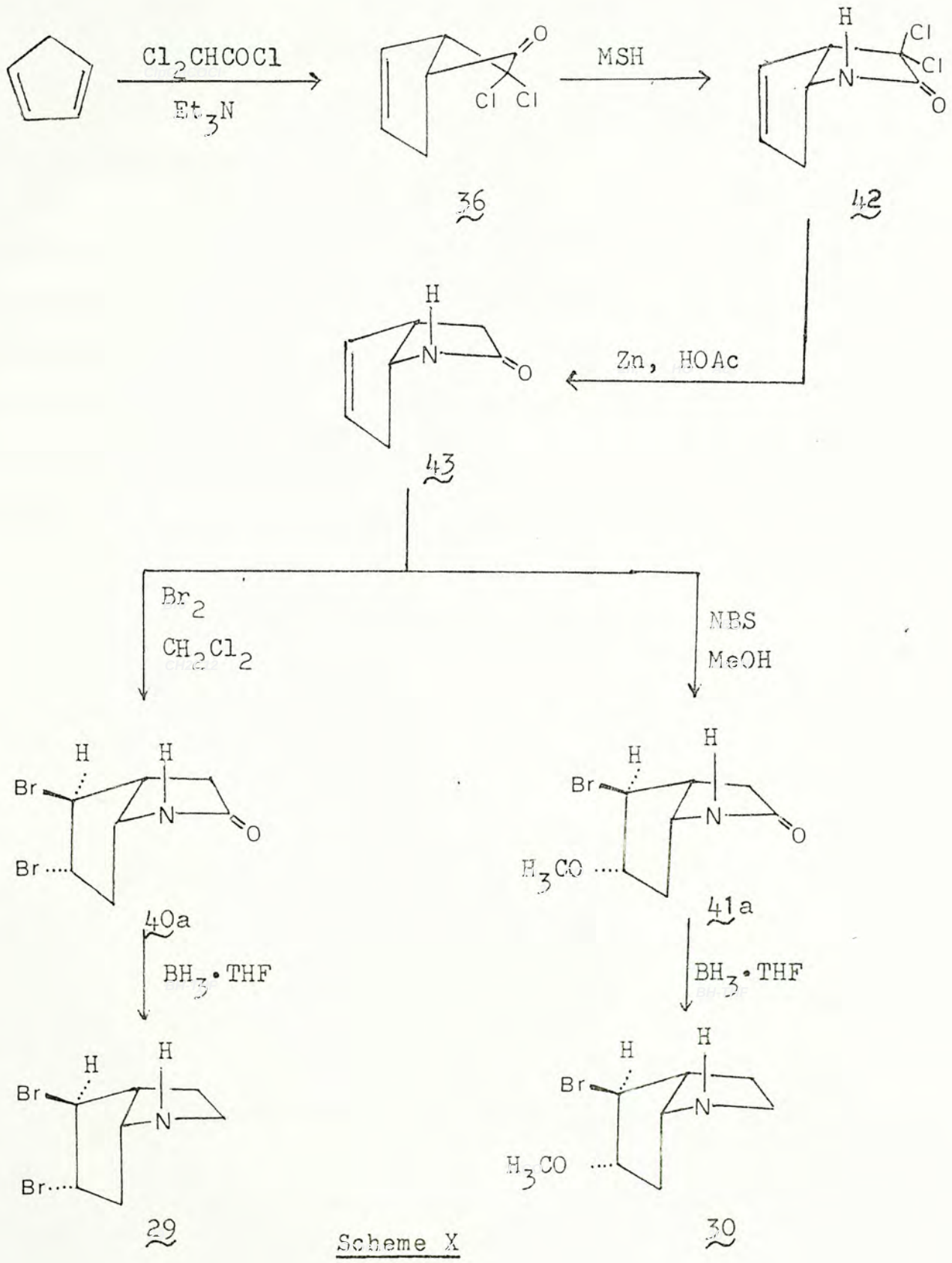
Scheme VIII



Scheme IX

We later discovered a much simplified route to achieve our goal without the formation of the 1-oxo isomeric lactam in the reaction of O-mesitylenesulfonylhydroxylamine (MSH)

with the unsymmetrical ketone 36 (Scheme X).

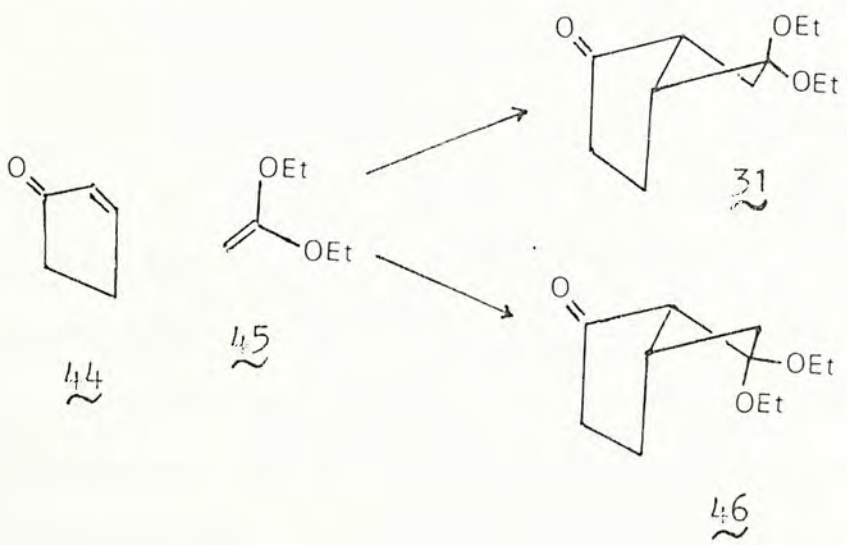


Scheme X

RESULTS AND DISCUSSIONS

I. Synthesis of 4-endo-methanesulfonyloxyoctahydropenta[b]pyrrole 27 and 4-endo-p-toluenesulfonyloxyoctahydropenta[b]pyrrole 28

It has been found[2] that the optimum conditions for obtaining the maximum yield of 6,6-diethoxybicyclo[3.2.0]-heptan-2-one (31) from the photochemical cycloaddition of cyclopentenone (44) and 1,1-diethoxyethene (45) was that the gram ratio of 44 to 45 was 1:10 and the time required was 3.75 h per gram of cyclopentenone.

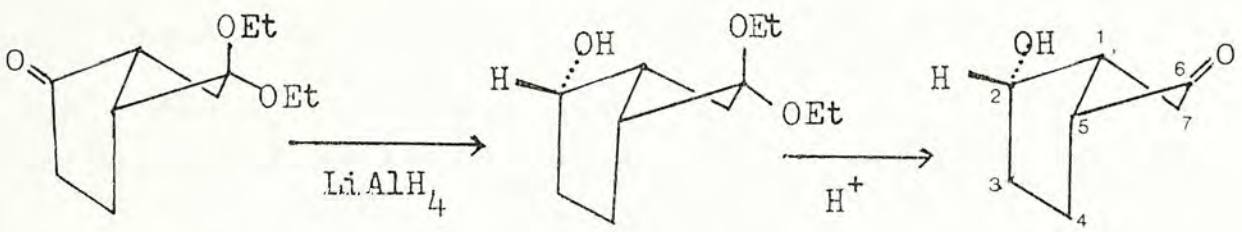


44 45 31 46

Furthermore, the isomeric product 46 was not obtained

and the regiospecificity of this photochemical cycloaddition reaction could be rationalized by means of the frontier molecular orbital theory.[17]

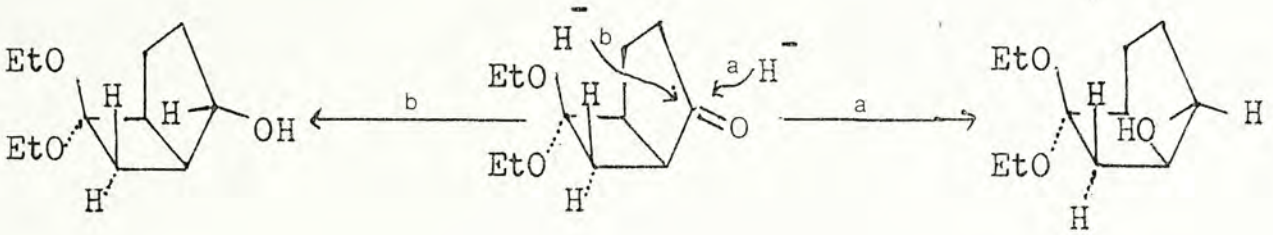
The hydroxy-ketal 47, obtained via lithium aluminium hydride reduction of 31, was hydrolyzed to the hydroxy-ketone 32 in 85% yield.



31 47 32

It was noted that the lithium aluminium hydride reduction of 31 had introduced an endo-hydroxyl group at the C-2 of 32. A close examination of the 3-dimensional structure of 31 revealed that the exo face is much less sterically hindered than the endo one, and therefore it was expected that the hydride ion should preferentially attack the carbonyl group from the exo site and hence the resulting hydroxyl group would be formed with an endo-configuration

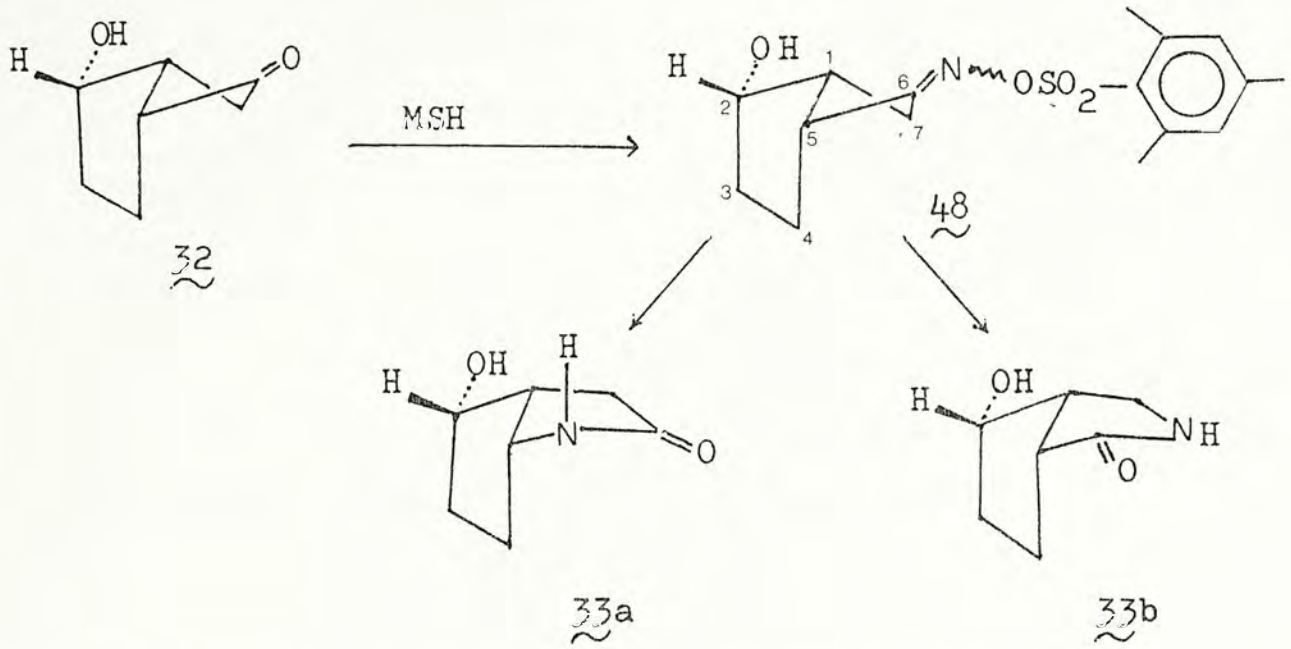
which was the desired stereoisomer for the synthesis described in the earlier section.



Chow[2] also found that both the classical Beckmann and Schmidt rearrangement of 32 was unsuccessful because the reaction conditions, when using these typical Beckmann reagents and Schmidt reagents, may be too drastic for the substrate. Later, he chose the highly reactive O-mesitylenesulfonylhydroxylamine (MSH)[18] as the reagent for the lactam formation because MSH reacts with ketones under very mild conditions to give the oxime mesitylenesulfonate in one step.

Treatment of 32 with O-mesitylenesulfonylhydroxylamine (MSH) at -10°C gave the oxime mesitylenesulfonate 48 which upon treatment with basic alumina in anhydrous methanol was converted to a mixture of hydroxy-lactams 33a and 33b

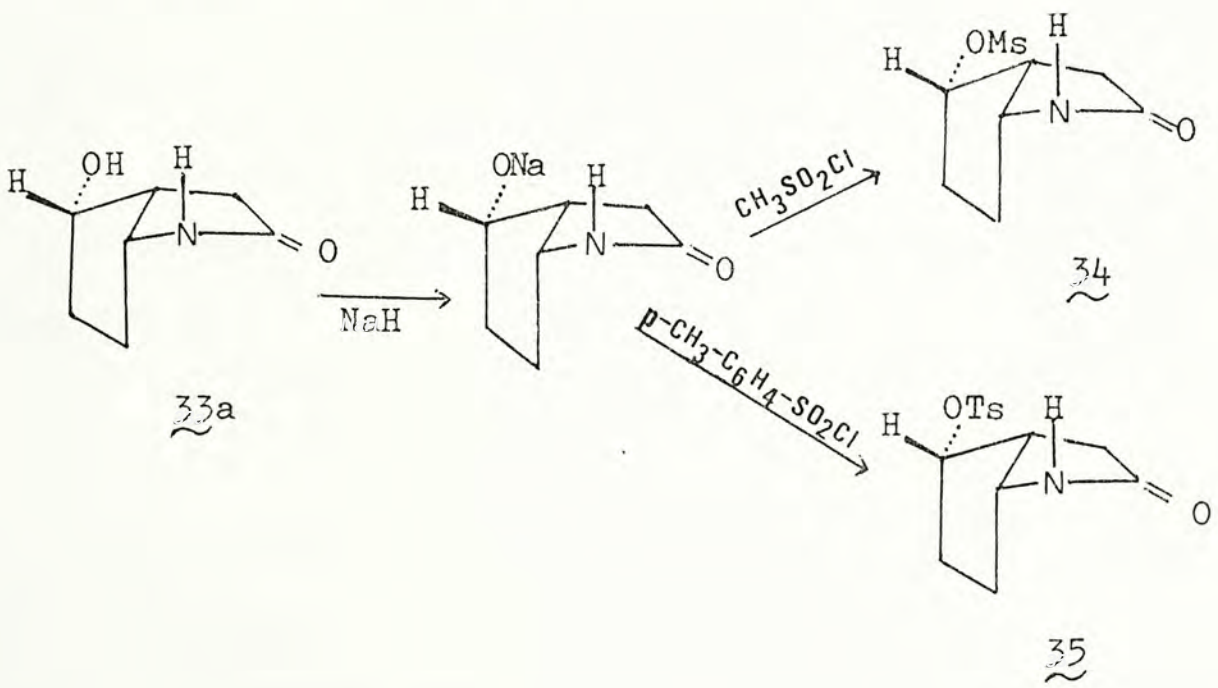
(3:1 ratio) in excellent yields. In this reaction, two



isomeric hydroxy-lactams were obtained because 32 is an asymmetrical ketone which can undergo methylene group or methine group migration in the Beckmann rearrangement. From the point of migratory aptitude, the shifting of the methine carbon (C-5) to give the desired lactam 33a should be more favorable than the migration of the methylene carbon (C-7) which yielded the other isomer 33b. Moreover, it has been found[2] that the regioselectivity of the lactam formation was shown to be temperature dependent. The ratio of 33a to 33b decreased with the increase of the reaction temperature.

The hydroxy-lactams 33a and 33b were readily soluble in alcohols and water. Compound 33a was separated from 33b by first recrystallization of the mixture from ethyl acetate, and then selectively crystallized from methanol.

By employing sodium hydride as a base to abstract the proton from the hydroxy-lactam 33a, the lactam-sulfonates 34 and 35 were prepared from the corresponding methanesulfonyl chloride and p-toluenesulfonyl chloride.



33a

34

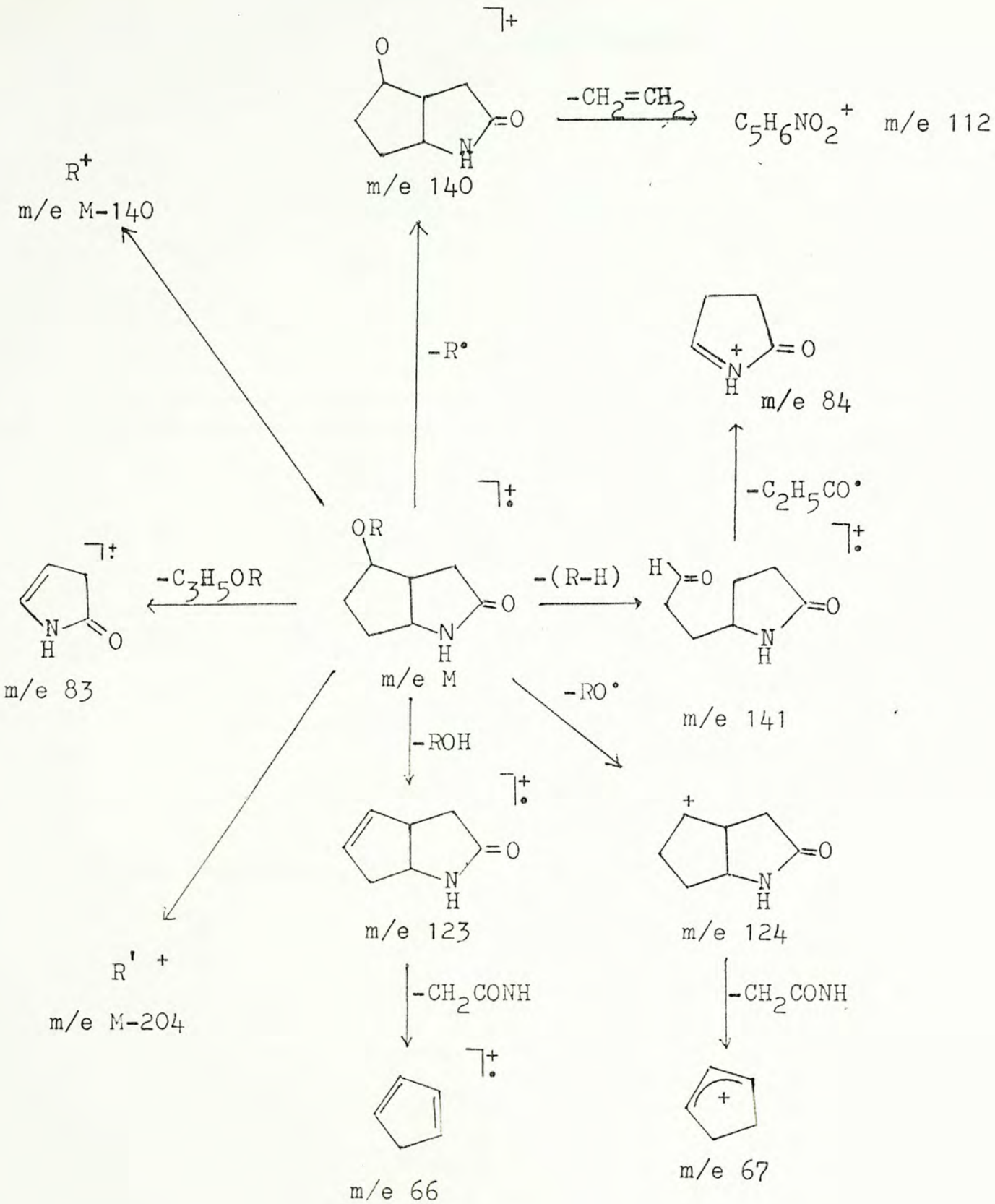
35

The hydroxy-lactam 33a was dissolved in hot tetrahydrofuran and was carefully added into a stoichiometric amount

of sodium hydride in dry tetrahydrofuran at room temperature. The solution was stirred at room temperature until the hydrogen evolution subsided. Methanesulfonyl chloride or p-toluenesulfonyl chloride which was dissolved in tetrahydrofuran was then added to yield the corresponding lactam-sulfonates 34 and 35. After chromatography, lactam-methanesulfonate 34 was recrystallized from chloroform to give needle-like crystals (mp 96-97°C) while lactam-p-toluenesulfonate 35 was recrystallized from pet. ether (40-60°C) and dichloromethane to give colorless crystals (mp 154-155°C).

The plausible mass spectral fragmentation of the bicyclic 4-endo substituted lactams 34 and 35 are summarized in Scheme XI. The relative abundance of the ions are tabulated in Table I.

The existence of a β-lactam was revealed by the high abundance of ions at m/e 84 and m/e 83 in all of the two compounds concerned. Elimination of ROH from 34 and 35 was one of the most prominent fragmentation pathways through


-CH2=CH2
C5H6NO2+
m/e 112
m/e 140
R+
m/e M-140
-R°
m/e 84
-C2H5CO°
-C3H5OR
-(R-H)
m/e 83
m/e M
m/e 141
-RO°
-ROH
m/e 123
m/e 124
R' +
m/e M-204
-CH2CONH
-CH2CONH
m/e 66
m/e 67

Scheme XI

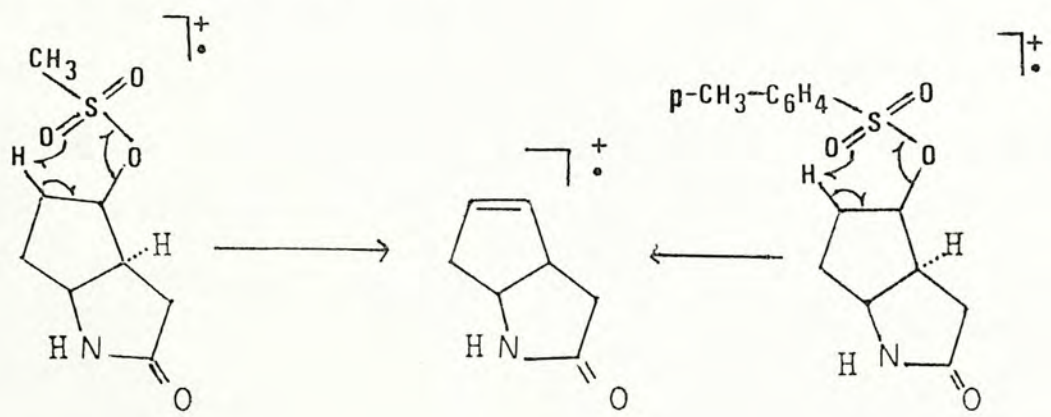
Table I. Relative abundance (%) of mass fragments of 34 and 35

m/e	M	M-140	M-204	141
34	5	22	0	1
35	29	34	100	2

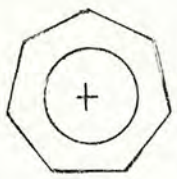
m/e	140	124	123	113
34	13	24	100	1
35	23	79	99	1

m/e	112	84	83	67	66
34	12	13	10	28	10
35	6	16	5	21	12

a McLafferty rearrangement.



Cleavage of the C-S bond in p-toluenesulfonyl group of 35 to yield a tropylium ion 49 to give m/e 91 was another fragmentation pathway. This accounted for the base peak of the mass spectrum of 35.



m/e 91

49

Compound 34 and 35 were reduced smoothly to give the amino-methanesulfonate 27 and the amino-p-toluenesulfonate 28 respectively by excess freshly prepared borane-tetrahydrofuranate.[19] The products were air-sensitive and quickly decomposed when exposed to atmosphere, and were also unstable towards silica gel. Attempts to chromatograph 27 and 28 led to decomposition. The crude 27 and 28 were preliminarily purified by dissolving the bicyclic amines 27 and 28 in 10% hydrochloric acid. Any non-basic insoluble materials were then filtered. The filtrate was neutralized carefully with solid sodium hydroxide at $0^{\circ}C$ and extracted three times with chloroform. The combined organic layers were dried and evaporated in vacuo to give the corresponding

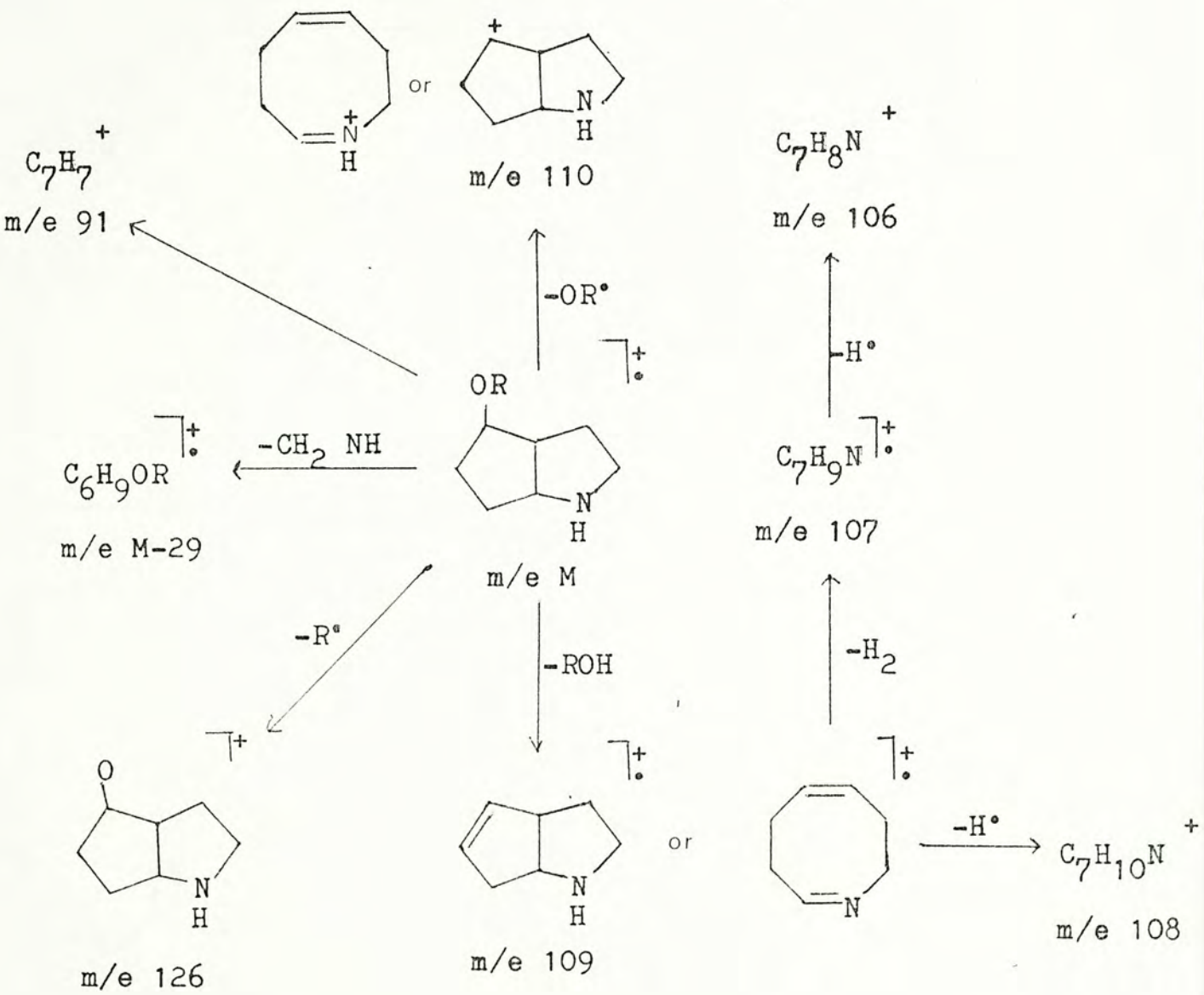
amines 27 and 28.

Both 27 and 28 were slowly solidified on refrigeration. The disappearance of the carbonyl absorption (1850-1600 cm^{-1}) indicated that both the lactams 34 and 35 were reduced respectively, the methanesulfonate and p-toluenesulfonate remained intact in compounds 27 and 28 and their ir spectra included absorption bands at 1360 and 1183 cm^{-1}.

The plausible mass spectral fragmentation of the bicyclic 4-endo substituted amines 27 and 28 are summarized in Scheme XII. The relative abundance of the ions are tabulated in Table II.

Contrary to the lactam-methanesulfonate 34 and lactam-p-toluenesulfonate 35, both the amino-methanesulfonate 27 and the amino-p-toluenesulfonate 28 favoured C_4-OR bond cleavage to give a prominent ion at m/e 110 (base peak), which may have a bicyclic structure or a rearranged skeleton 50.

Again, the C-S bond cleavage of the p-toluenesulfonyl


or
$C_7H_7^+$
m/e 91
m/e 110
$C_7H_8N^+$
m/e 106
-OR°
-H°
OR
-CH_2 NH
$C_6H_9OR^{+\cdot}$
m/e M-29
$C_7H_9N^{+\cdot}$
m/e 107
m/e M
-R°
-ROH
-H_2
O
N
H
m/e 126
m/e 109
or
-H°
$C_7H_{10}N^+$
m/e 108

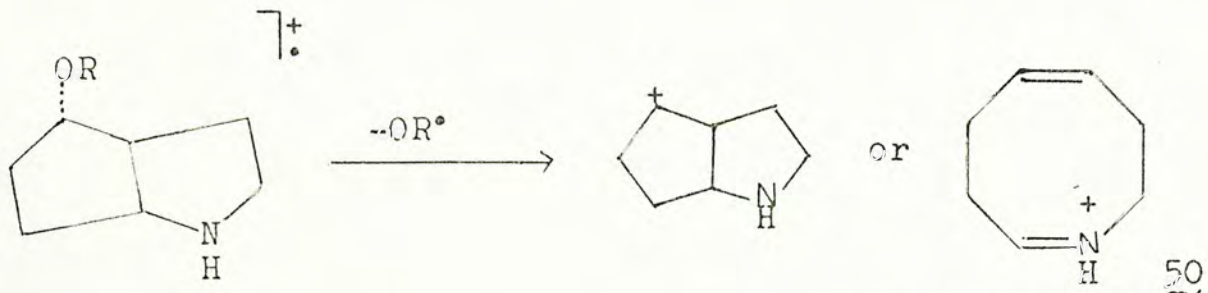
Scheme XII

Table II. Relative abundance (%) of mass fragments of 27 and 28

m/e	M	M-29	126	110
27	0	30	13	100
28	1	0	6	100

m/e	109	108	107	106
27	25	31	3	4
28	20	21	7	3

m/e	91
27	0
28	93

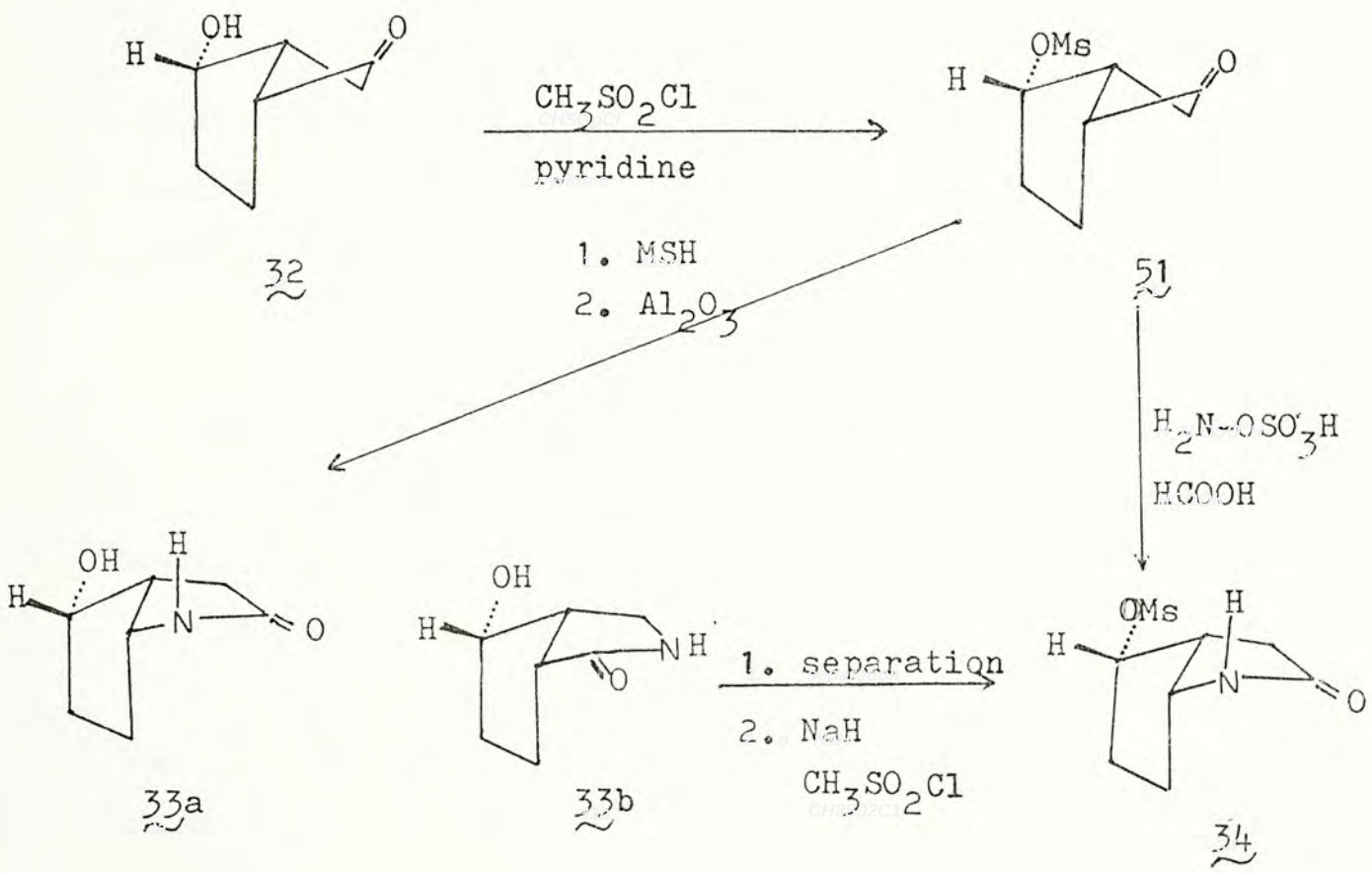


50

m/e 110 (100%)

group in compound 28 gave a stable tropylium ion 49 (m/e 91) which was absent in the mass spectrum of 27.

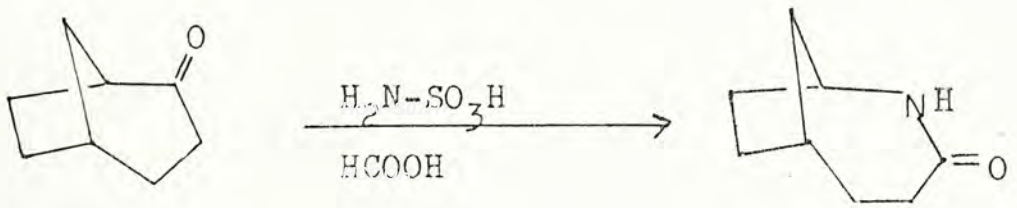
Starting from the hydroxy-ketone 32, synthesis of the lactam-methanesulfonate 34 via other alternative routes have also been attempted (Scheme XIII).



Scheme XIII

Reaction of methanesulfonyl chloride with 32 in the presence of pyridine gave an excellent yield (78%) of 2-methanesulfonyloxybicyclo[3.2.0]heptan-6-one (51) which reacted with excess MSH at -10°C to give a mixture of two isomeric hydroxy-lactams 33a and 33b instead of a mixture of isomeric lactam-methanesulfonates. It was because under basic conditions, the leaving group, i.e. methanesulfonate group, readily solvolyzed to yield the hydroxyl group. Similar to the earlier case, the desired lactam 33a was separated from 33b by recrystallization, and in the presence of sodium hydride, 33a reacted with methanesulfonyl chloride to give 34.

Recently, it has been found[20] that the bicyclo[3.2.1]octan-2-one (52) was converted to the lactam 53 exclusively in one-step with hydroxylamine-O-sulfonic acid and formic acid.[21]

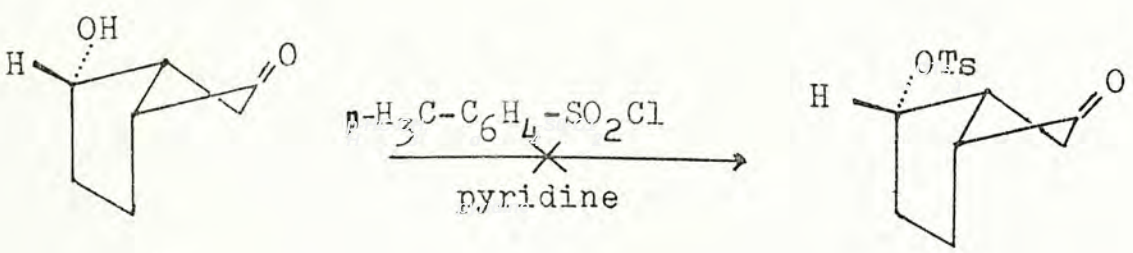


52 (>95%) 53

Selective methine group migration of the oxime intermediate

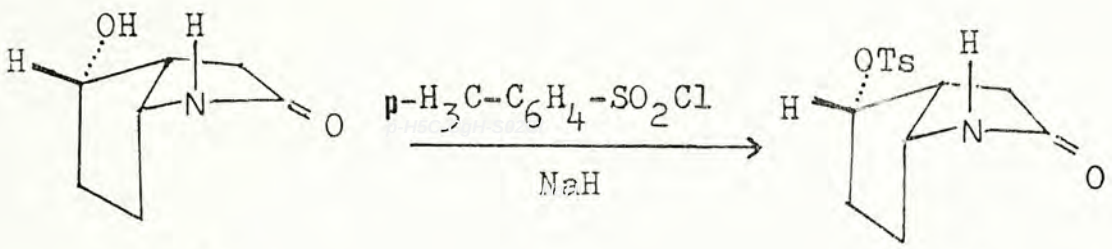
gave rise to the lactam 53 exclusively. We have applied this method to test if the lactam-methanesulfonate 34 was produced regiospecifically. Thus, compound 51 was treated with hydroxylamine-O-sulfonic acid in formic acid and the solution was heated at 60°C for 5 h. After neutralization, extraction and finally evaporation, compound 34 was obtained exclusively in 20% yield. The disadvantage of this method was that the yield was low (only 20%), whereas MSH gave at least 70% yield of the lactam product. So in our later Beckmann rearrangement of ketones, route via MSH was preferred.

Contrary to the reaction of methanesulfonyl chloride with the bicyclic hydroxy-ketone 32, p-toluenesulfonyl chloride did not react with 32 in the presence of pyridine to give the corresponding p-toluenesulfonate 54. The failure



32 54

of this reaction was originally thought to be due to the sterically hindrance of the endo-hydroxyl environment. However, the hydroxy-lactam 33a which is structurally similar to 32 reacted smoothly with p-toluenesulfonyl chloride in the presence of sodium hydride to give 35.



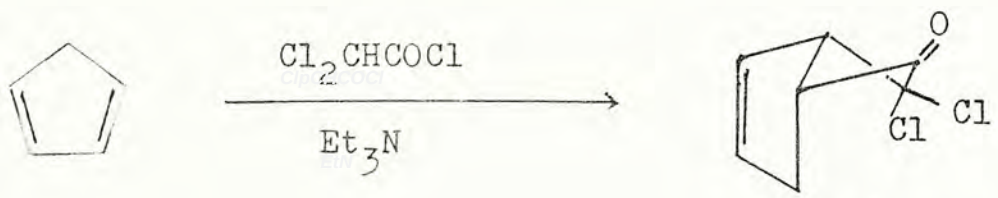
33a 35

In order to account for the difference between these two reactions, two factors affecting the nucleophilic reactions were indeed operative. One was the steric effect while the other was the electronic effect which was related to the nucleophilicity of the substrate. Both steric and electronic effect were unfavorable in the reaction of 32 and p-toluenesulfonyl chloride which prohibited any reaction. In the reaction of 33a with p-toluenesulfonyl chloride, although steric effect remained as an unfavourable condition, electronic effect was favourable because abstraction of

the proton from the hydroxyl group of 33a by sodium hydride increased the nucleophilicity of the substrate and hence completed the transformation.

II. Synthesis of 4-exo-5-endo-dibromooctahydropenta[b]-pyrrole 29 and 4-exo-bromo-5-endo-methoxyoctahydropenta[b]-pyrrole 30

The starting point of this synthetic scheme was the regiospecific addition of dichloroketene to cyclopentadiene. It has been found[16] that treatment of a solution of cyclopentadiene and dichloroacetyl chloride in dry hexane at 0°C with an excess of dry triethylamine in hexane gave 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one 36 in good yield.



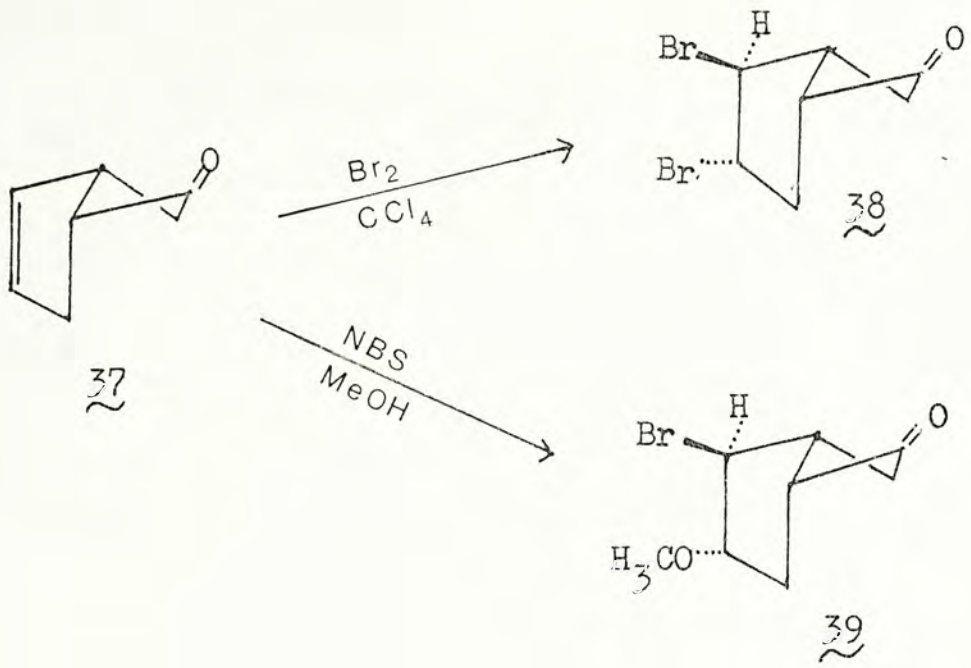
36

The cycloaddition of ketenes to double bonds has received considerable attention.[22] These reactions went smoothly when the ketenes carried electron-withdrawing

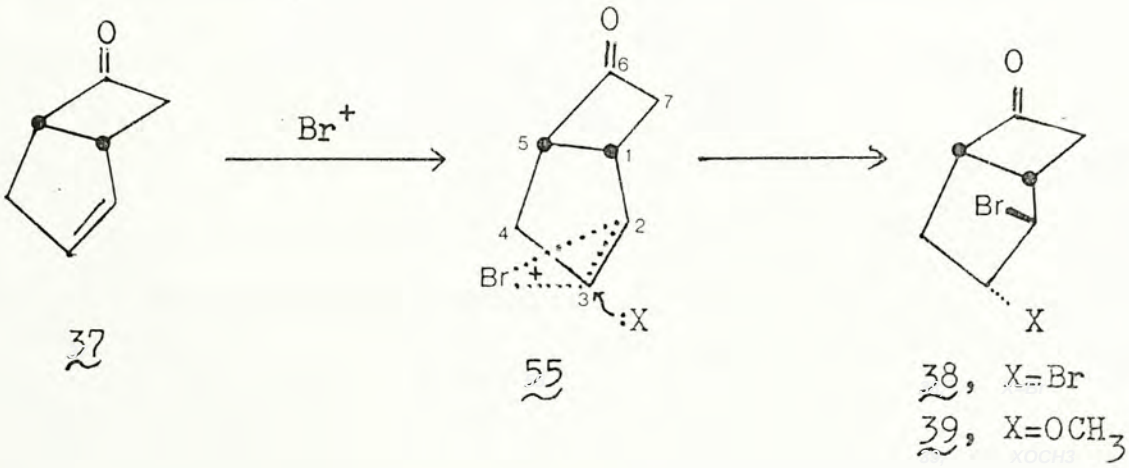
groups (e.g. Cl) and when the olefins were relatively electron-enriched. The electron-withdrawing groups lowered the energy of the LUMO of the ketenes, and the electron-enriched olefins have a higher-energy HOMO. The important interaction would therefore be HOMO(ketenophile)/LUMO(ketene). Again, the regioselectivity of these reactions could also be rationalized by means of the frontier molecular orbital theory.[17]

Dechlorination of 36[16] was effected in excess of zinc dust in glacial acetic acid at about 70°C for approximately 1 h to afford the bicyclo[3.2.0]hept-2-en-6-one 37 in very high yield (>90%).

It has also been found[15] that reaction of 37 with bromine in carbon tetrachloride at 0°C (buffered in the presence of sodium bicarbonate suspension) gave 2-exo-3-endo-dibromo-bicyclo[3.2.0]heptan-6-one (38) in high yield. Similarly, reaction of an equimolar quantity of N-bromosuccinimide (NBS) with 37 in methanol gave 2-exo-bromo-3-endo-methoxy-bicyclo-[3.2.0]heptan-6-one (39) in 85% yield.



The additions to the double bond of bicyclo[3.2.0]hept-2-en-6-one 37 reported above were stereospecific. This was rationalized by postulating the preferential formation of the exo-bromonium ion intermediate 55 which was attacked from the endo-face by the attendant nucleophile at the less-hindered C-3 position.

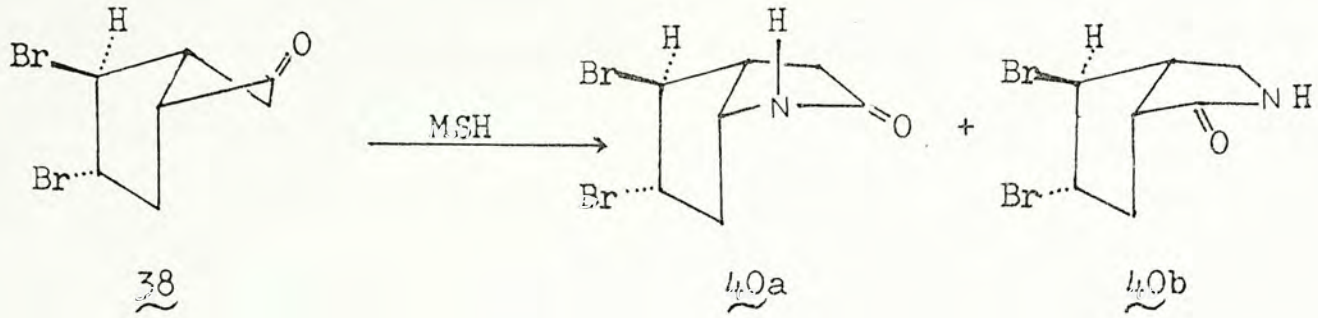


37

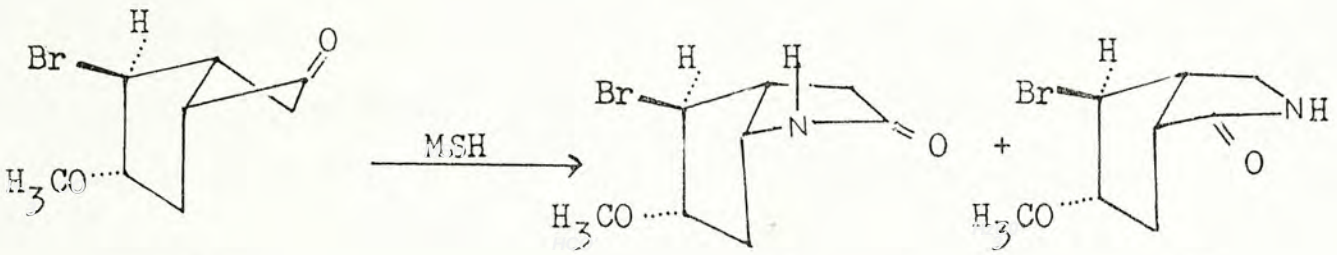
55

38, X=Br

39, X=OCH3



38 40a 40b



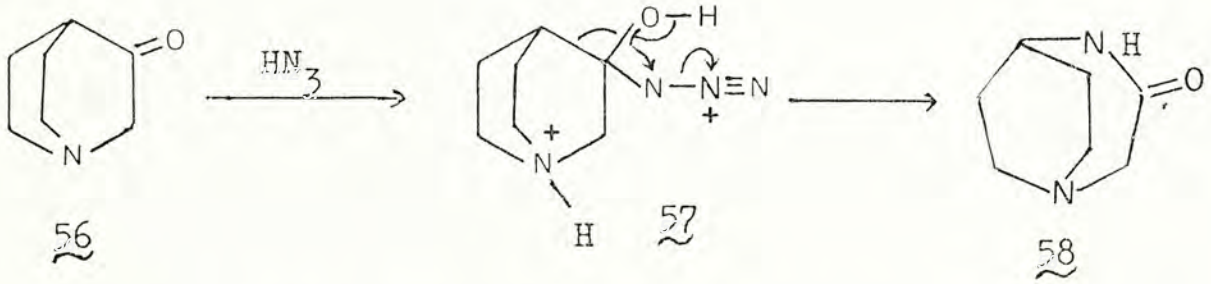
39 41a 41b

The reaction of 38 with excess MSH at -10°C gave a mixture of isomeric lactam-dibromides 40a and 40b (3:1 ratio) in 71% yield. The ir spectrum of the mixture revealed the presence of a γ-lactam (1684 cm^{-1}) function. The desired isomer 40a was separated from 40b by chromatography and gave colorless crystals (mp 150-152°C) after recrystallization from benzene.

In a similar manner, compound 39 was converted to the

lactam-methoxybromides 41a and 41b in 75% yield. However, unlike the lactam-dibromides, neither chromatography nor recrystallization could separate the desired isomer 41a from 41b.

It was found[23] that when 1-azabicyclo[2.2.2]octan-3-one (56) was treated with hydrazoic acid, a single azalactam 58 was obtained in good yield which was resulted exclusively from the migration of the methine carbon-carbon bond most distant from the ring-nitrogen atom. This was because in the intermediate 57, the strong electron-attracting

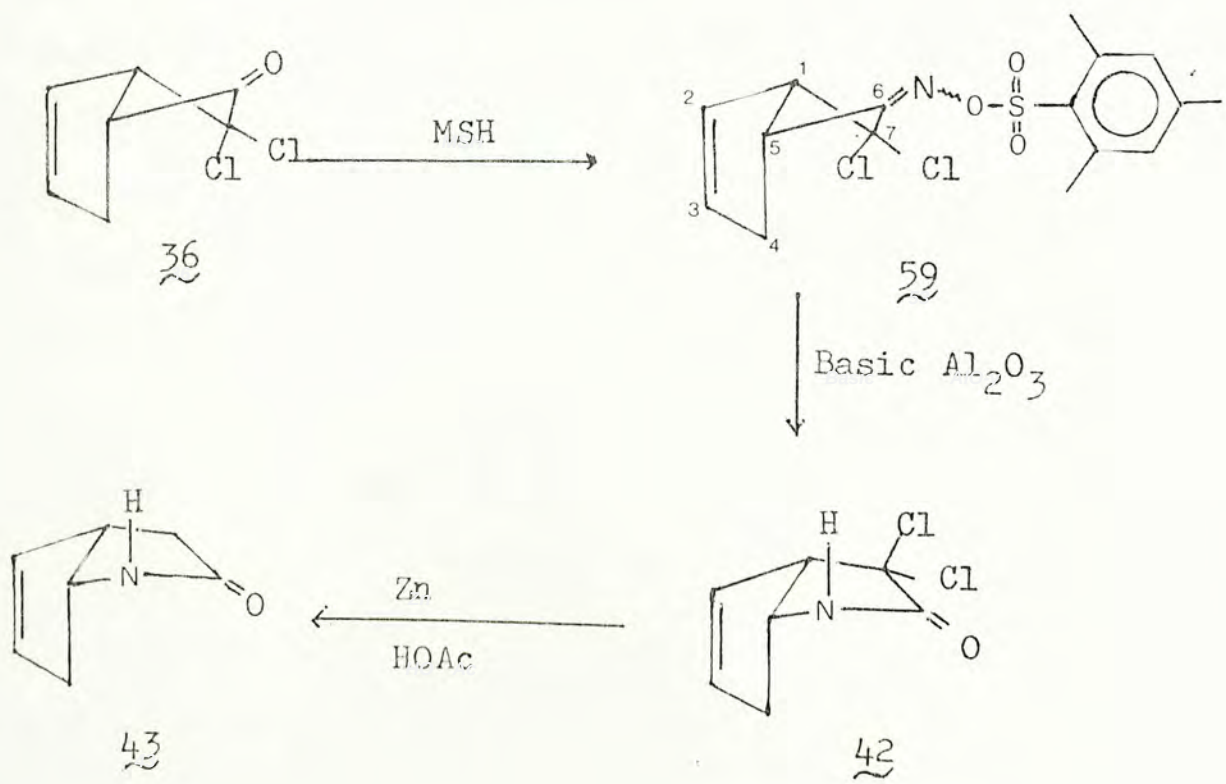


56 57 58

characteristics of the protonated ring-nitrogen were seen to reduce the migratory aptitude of the neighbouring carbon-carbon σ bond (methylene carbon) to the electron-deficient azide nitrogen. The operation of this inductive effect permitted the preferential rearrangement of the methine carbon-carbon σ bond. The exclusive formation of 58 supported this hypothesis.

On the basis of the above observation, we planned a stereospecific synthesis of the two 2-oxo lactam products 40a and 41a without the formation of their corresponding 1-oxo isomeric lactam products 40b and 41b in the Beckmann rearrangement.

Treatment of 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one 36 with excess MSH at room temperature afforded only one lactam-dichloride product 42, which was resulted exclusively from bridged head migration (C-5), as shown by the seven characteristic peaks in its ^{13}C-nmr.

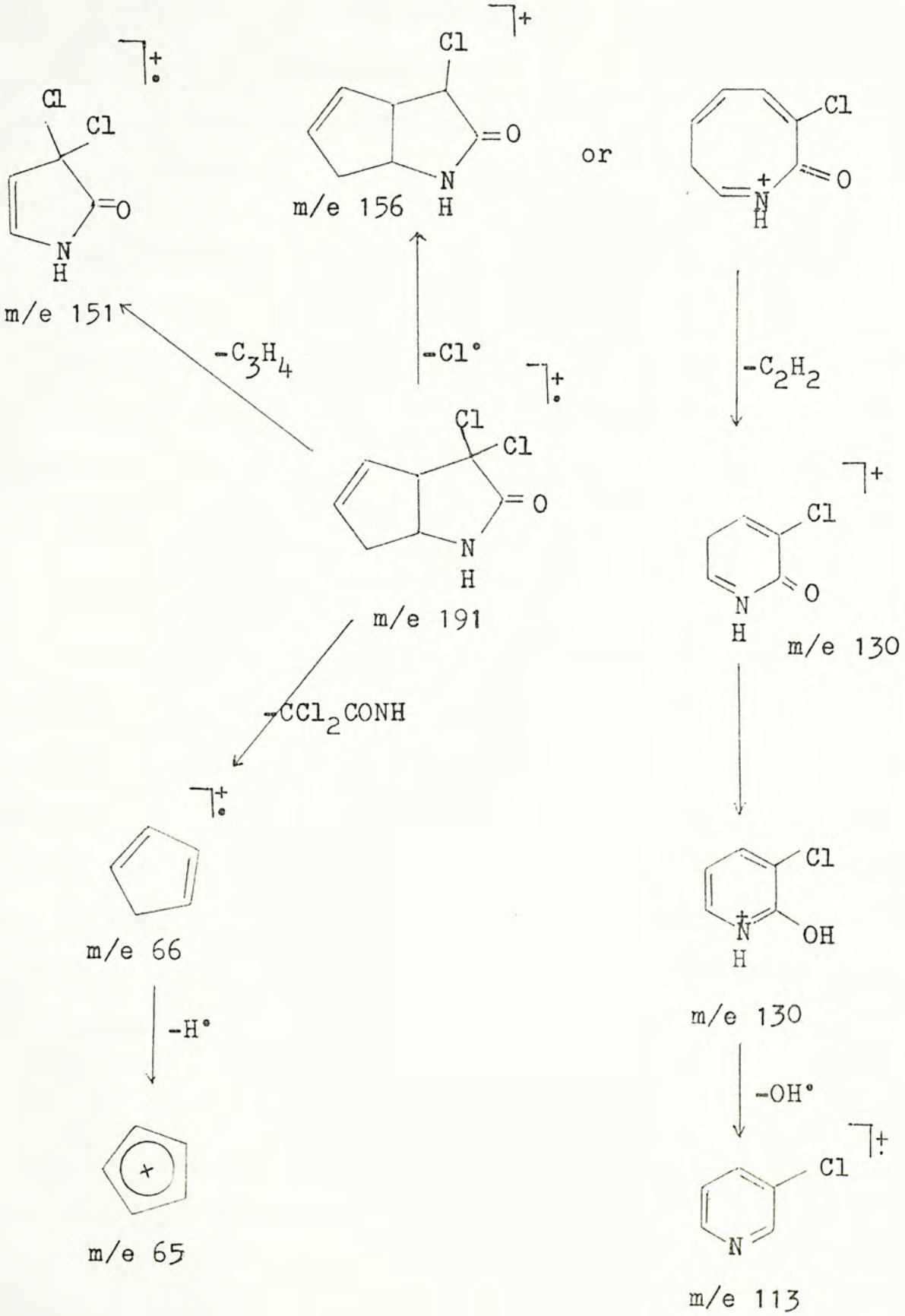


36 59 43 42

Similar to 57, the two strong electronegative groups (Cl group) in the methylene carbon (C-7) reduced its migratory aptitude to the nitrogen in the oxime-mesitylenesulfonate intermediate 59 and permitted the preferentially migration of methine carbon (C-5), and consequently, only the 2-oxo isomeric lactam-dichloride 42 was obtained.

After chromatography, compound 42 was then recrystallized from pet. ether (40-60°C) and dichloromethane to give colorless crystals (mp 138-140°C). Its ir spectrum included, in addition to a broad N-H absorption around 3200-3500 cm^{-1}, a strong absorption at 1727 cm^{-1} which is the characteristic of a lactam carbonyl group with adjacent carbon containing electronegative groups that shift the absorption to higher wave number. The mass spectrum of 42 revealed a molecular ion (M) at m/e 191. Two chlorine atoms in the molecule was reflected by the ratio of 10:6:1 in M, M+2 and M+4 molecular ions respectively. The plausible fragmentation patterns are summarized in Scheme XIV.

Elimination of a chlorine radical from the parent ion was confirmed by the presence of peaks at m/e 156 and


m/e 151
m/e 156
or
m/e 191
m/e 130
m/e 66
m/e 65
m/e 130
m/e 113
-C3H4
-Cl°
-C2H2
-CCl2CONH
-H°
-OH°

Scheme XIV

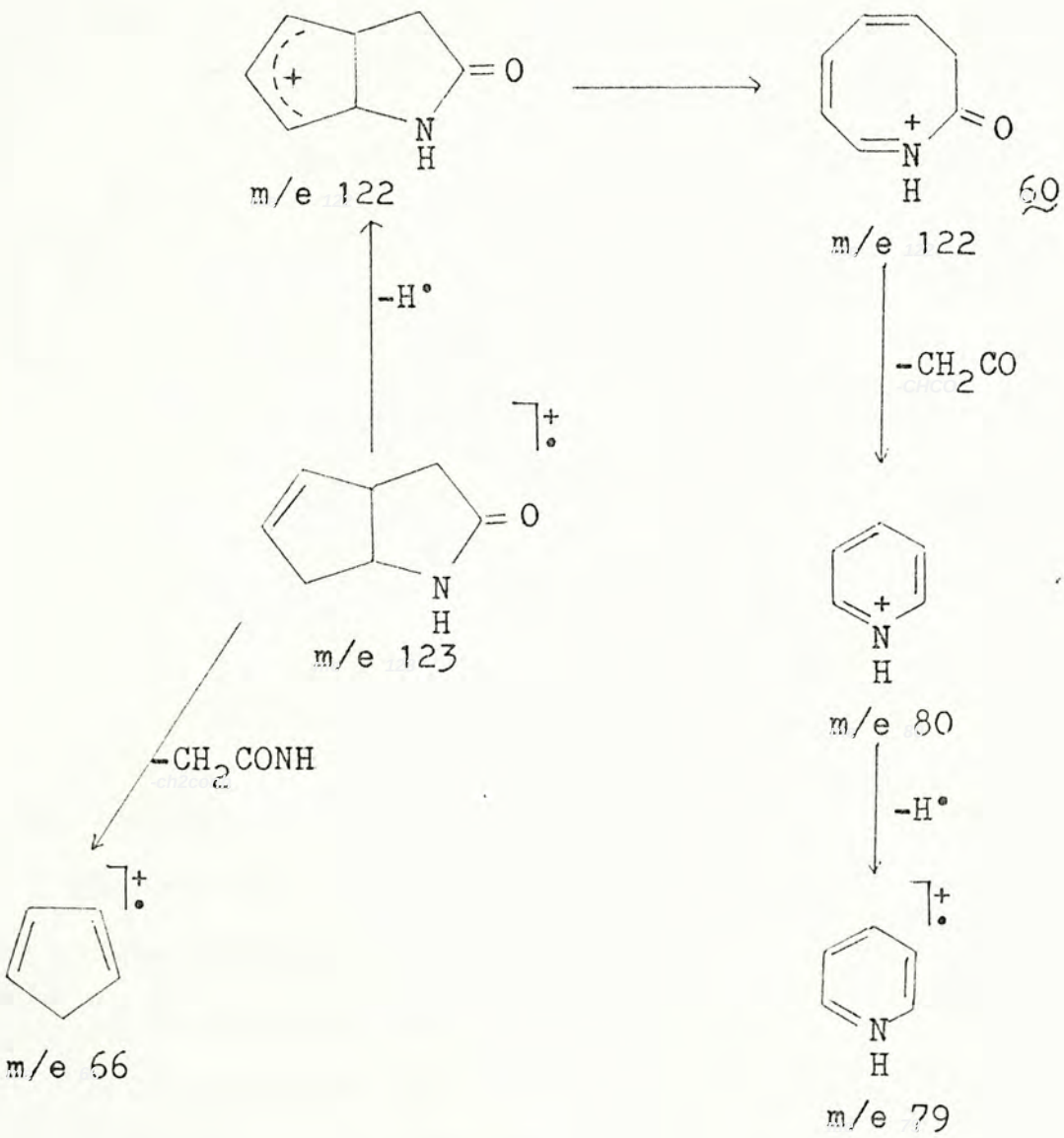
m/e 158 (ratio 3:1). The base peak at m/e 113, a 3-chloropyridinium ion, was produced through a successive loss of C_2H_2 and OH radical from the m/e 156 species.

Dechlorination of 42 was also effected in excess of zinc dust in glacial acetic acid at about 70°C for approximately 1 h to afford the 2-oxo-hexahydrocyclopenta-4-en[b]pyrrole (43) in high yield (89%). It was also noted that the amide group of 42 remained intact during the course of the dehalogenation reaction.

Compound 43 was recrystallized from pet. ether (40 -60°C) and dichloromethane to give needle-like crystals (mp 114-116°C). The nmr signal at δ 5.5-6.0 was attributed to the olefinic protons. The broad absorption from δ 8.5 to 7.6 was due to the acidic hydrogen of the lactam moiety. The ir spectrum of 43 showed a broad N-H absorption around 3400-3200 cm^{-1} and a strong absorption peak at 1683 cm^{-1}, a characteristic of lactam carbonyl group.

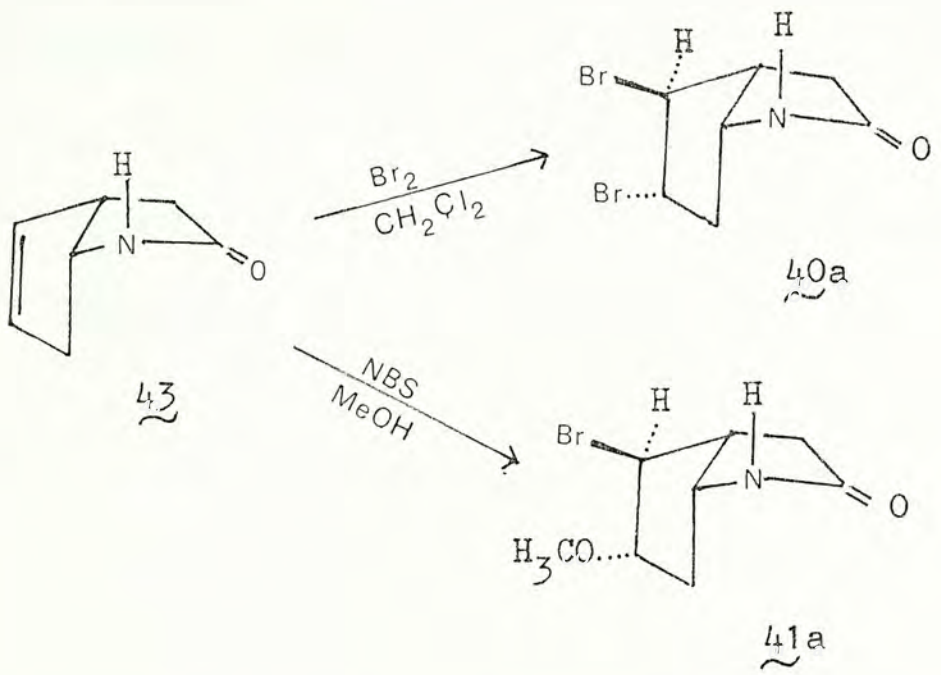
The mass spectrum of 43 showed the parent ion, which was also the base peak, at m/e 123 with other prominent

ions at m/e 80, m/e 79, and m/e 66. Elimination of a hydrogen radical from the molecular ion m/e 123 gave a keto-azacyclooctatriene cation 60 which upon the sequential loss of CH_2CO and H° generated ions at m/e 80 and m/e 79 respectively (Scheme XV).



Scheme XV

Bromination of 43 in dichloromethane and in methanol gave the lactam-dibromide 40a and lactam-methoxybromide 41a, respectively. After chromatography and then recrystallization from benzene, both lactams 40a and 41a afforded colorless crystals.



For the lactam-methoxybromide 40a, its nmr spectrum exhibited a sharp singlet at δ 3.4 for 3H which was attributed to the methoxy protons. The broad absorptions at δ 8.1 to 7.6 in both nmr spectra of 40a and 41a were due to the acidic hydrogens of the lactam moiety. Both lactams also showed a broad N-H absorption around 3500-3200 cm^{-1} and a strong absorption peak at 1680 cm^{-1},

a characteristic of a β-lactam carbonyl group, in their corresponding ir spectra.

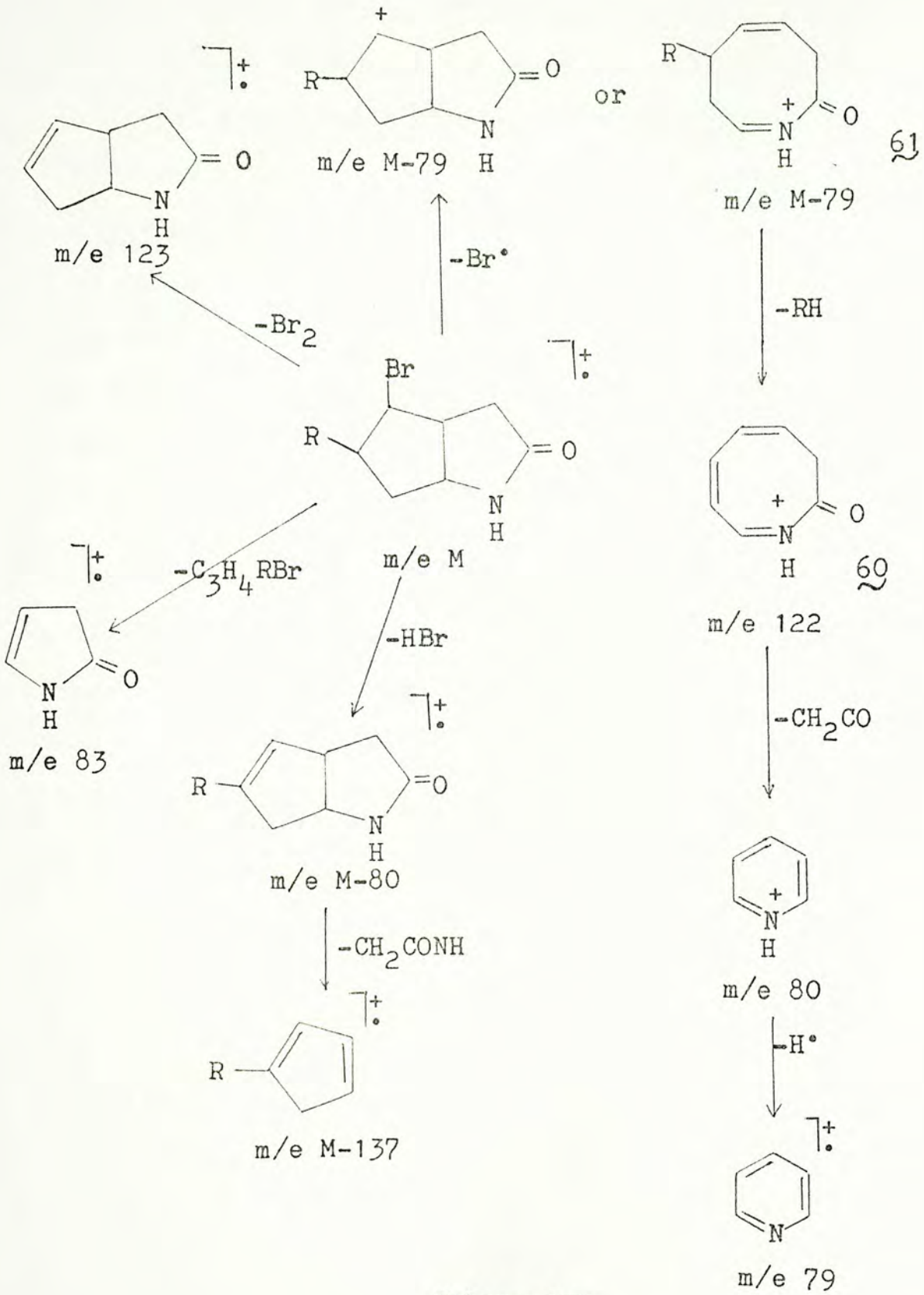
The plausible mass spectral fragmentation of the bicyclic 4-exo-5-endo substituted lactams 40a and 41a are summarized in Scheme XVI. The relative abundance of the ions are tabulated in Table III.

Table III. Relative abundance (%) of mass fragments of 40a and 41a

m/e	M	M-79	M-137	123
40a	0	100	0	27
41a	0	82	100	4

m/e	122	83	80	79
40a	13	16	33	41
41a	19	5	13	18

Again, the existence of a β-lactam was revealed by


m/e 123
m/e M-79
or
m/e M-79
61
-Br•
-Br2
-RH
m/e M
m/e 122
60
-C3H4RBr
-HBr
-CH2CO
m/e 83
m/e M-80
m/e 80
-CH2CONH
-H•
m/e M-137
m/e 79

Scheme XVI

the high abundance of ion at m/e 83, especially in the spectrum of 40a. Cleavage of the C_4-Br bond of 40a and 41a to eject a bromine radical to give the corresponding m/e M-79 was a major fragmentation pathway which generated the keto-azacyclooctadiene cation 61. With the expulsion of HBr or MeOH moeity, cation 61 gave a keto-azacycloocta-triene cation 60 which was identical to the fragment ion from 43 as discussed earlier to give the ion at m/e 80 and the pyridinium ion (m/e 79).

Excess borane-tetrahydrofuranate was used to reduce the lactam-dibromide 40a and lactam-methoxybromide 41a to produce the corresponding amino-dibromide 29 and amino-methoxybromide 30. Similar to the amino-methanesulfonate 27 and the amino-p-toluenesulfonate 28, both 29 and 30 were air sensitive, unstable to silica gel and decomposed when vacuum distilled. Acid purification was used to eliminate any non-basic side products in crude 29 and 30.

While the amino-dibromide 29 slowly solidified on refrigeration, the amino-methoxybromide 30 remained

as a viscous oil. The disappearance of the lactam carbonyl absorption in their ir spectra indicated both the lactams 29 and 30 have been reduced.

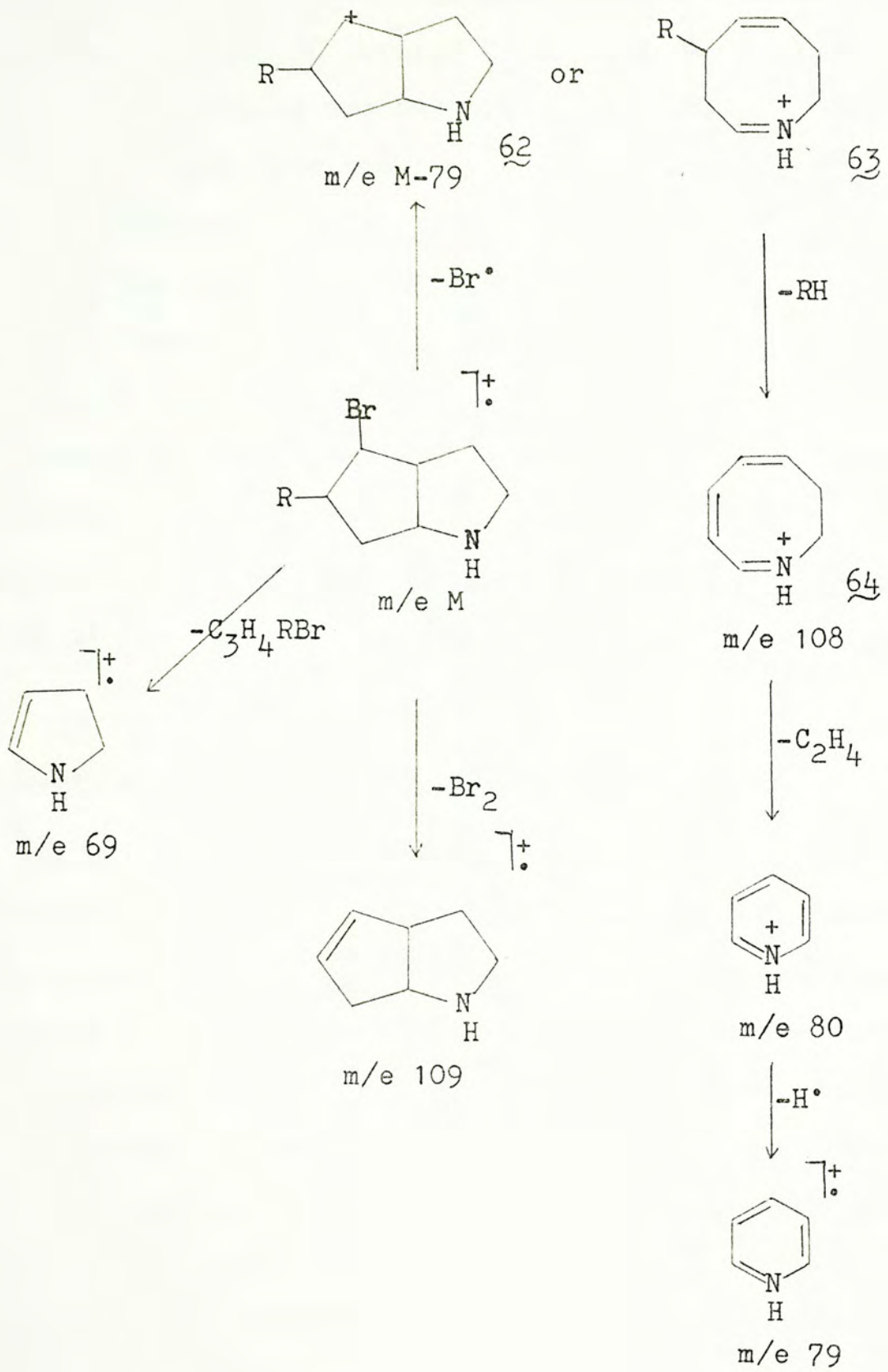
The plausible mass spectral fragmentation of these two bicyclic 4-exo-5-endo substituted amines 29 and 30 are summarized in Scheme XVII. The relative abundance of the ions are tabulated in Table IV.

Table IV. Relative abundance (%) of mass fragments of 29 and 30

m/e	M	M-79	109	108
29	0	100	36	31
30	0	100	9	16

m/e	80	79	69
29	17	13	64
30	13	10	17

Similar to the lactam-dibromide 40a and the lactam-

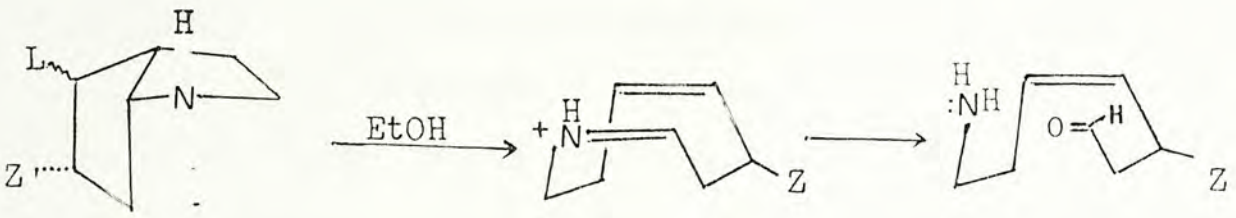

R
or
R
62
63
m/e M-79
-Br°
-RH
Br
R
m/e M
64
m/e 108
-C3H4RBr
-C2H4
-Br2
m/e 69
m/e 80
-H°
m/e 109
m/e 79

Scheme XVII

methoxybromide 41a, both the amino-dibromide 29 and the amino-methoxybromide 30 favored C_4-Br bond cleavage to give the corresponding m/e M-79 ions. Elimination of a HBr or MeOH moiety from the bicyclic cation 62 or the rearranged isomeric 4-substituted azacyclooctadiene cation 63 yielded the azacyclooctatriene cation 64 at m/e 108. Sequential loss of C_2H_4 and H radical from 64 led to the formation of ions at m/e 80 and m/e 79 which are characteristic of the whole series of the compounds under study. Besides, elimination of a bromine molecule from the molecular ion M to give an ion at m/e 109 was also a significant fragmentation pathway of 29.

III. Solvolytic studies of 28, 29 and 30

The solvolysis of 28, 29 and 30 have been carried out in ethanolic solution under similar conditions. Iminium ion is known to be highly unstable in acidic media, readily hydrolyzed in aqueous solutions to give an aldehyde or ketone together with the amino function. Because of this reason, excess of base (e.g. sodium hydride, 2,2,6,6-tetramethyl-4-piperidinol or sodium carbonate) was added to neutralize the acid (e.g. p-toluenesulfonic acid or hydrobromic acid) generated during the solvolytic process.



28, L=endo-OTs, Z=H
29, L=exo-Br, Z=Br
30, L=exo-Br, Z=OCH_3

In one attempt, potassium tetrachloroplatinate (II) (K_2PtCl_4) was added in the hope that the possible 3,4,7,8-tetrahydroazocine 2a produced from the solvolysis may be trapped as a transition metal complex. Solvolysis of the amino-p-toluenesulfonate 28 in 80% ethanol, in the presence of K_2PtCl_4 and sodium carbonate was heated under reflux for 10 h in nitrogen atmosphere. It was noted that the mixture turned into platinum black after ½ h. The crude product exhibited no olefinic proton in the nmr spectrum. The p-toluenesulfonate group was cleaved as indicated by the disappearance of the singlet methyl absorption at δ 2.5 in the proton nmr spectrum. The structure of the product was yet unidentified.

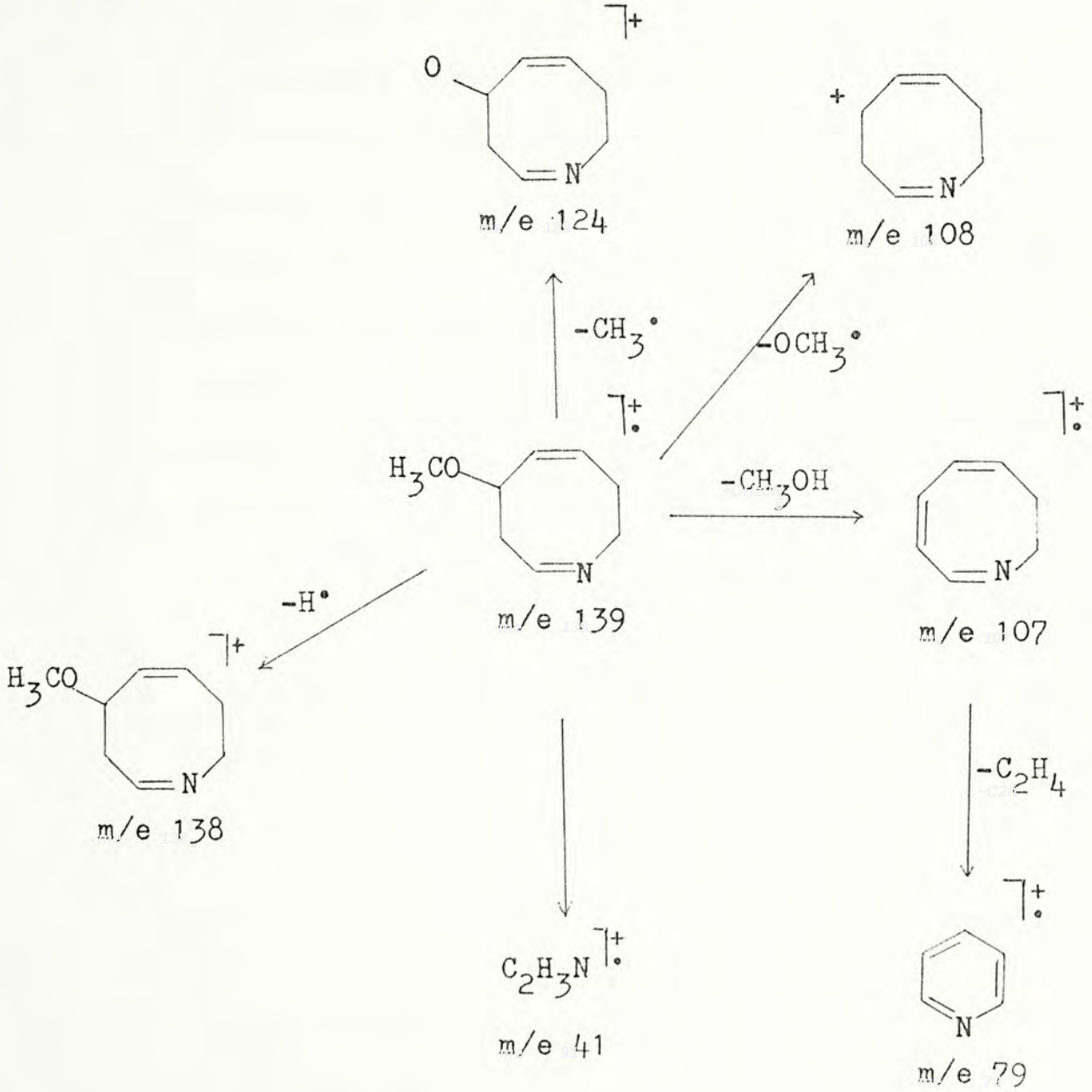
In contrast, the solvolysis of 28 in the presence of

sodium hydride in dry tetrahydrofuran produced different results. The p-toluenesulfonate group remained un-solvolysed. Inspection of the proton nmr indicated that the reaction product was only the starting material.

Solvolytic studies of 29 and 30 in absolute ethanol and in 80% ethanol respectively in the presence of 2,2,6,6-tetramethyl-4-piperidinol were not promising. After work up, proton nmr indicated that the starting materials 29 and 30 were recovered in both cases.

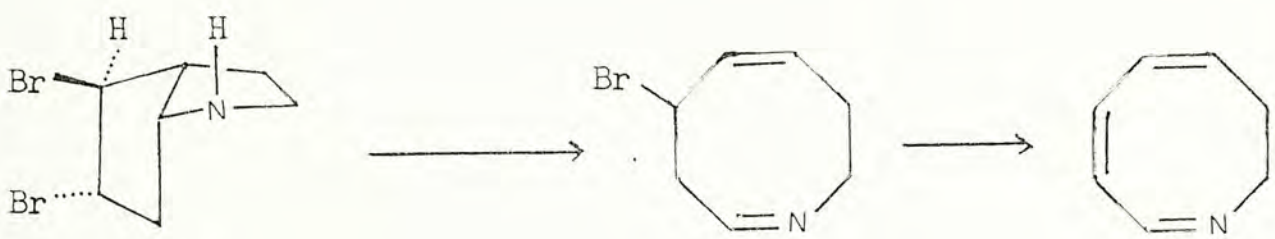
The solvolysis of 30 in the presence of sodium hydride in tetrahydrofuran gave different results. The crude product exhibited an absorption signal at δ 8.5-8.3 as well as olefinic protons at δ 6.2-5.6 in the proton nmr spectrum. The methoxy group was also observed as a sharp singlet at δ 3.4 in the nmr spectrum. GC-MS revealed 3 components in the reaction products. The mass spectrum of the second component (retention time 13 min) was most promising, because the molecular ion and the fragment ions were consistent with the fragmentation (Scheme XVIII) of 4-methoxy-3,4,7,8-tetrahydroazocine 2c; ms (m/e) for the second component: 139(36%), 138(14%), 124(38%),

108(100%), 107(29%), 106(43%), 79(58%), 77(27%), 59(41%), 55(21%), 53(19%) and 41(51%). However, isolation of the pure component by preparative GC and further proof of its structural identity is required.



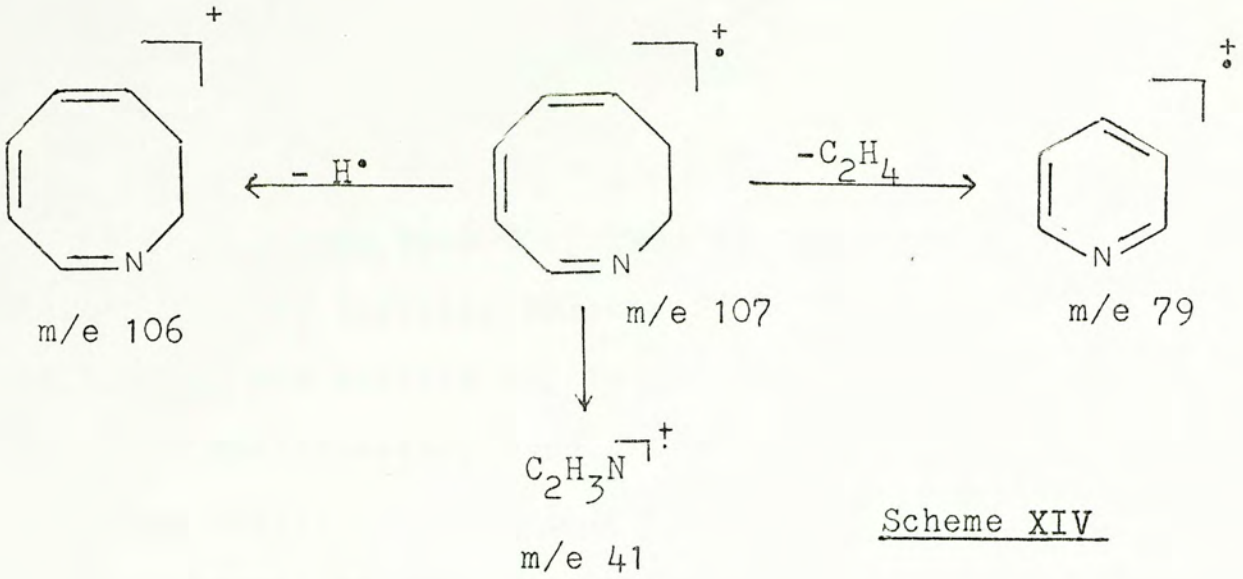
Scheme XVIII

Similar to 30, the solvolysis of 29 in the presence of excess sodium hydride in dry tetrahydrofuran gave results that were different from that in ethanol. The crude product gave an absorption signal at δ 8.5-8.3 and signals due to olefinic protons at δ 6.2-5.5 in the proton nmr spectrum. GC-MS of the product revealed 2 components. The mass spectrum of the first component (retention time 5.5 min) revealed that it was likely to be 7,8-hexahydroazocine (65) which may arise from further trans elimination of the expected product, 4-bromo-3,4,7,8-tetrahydroazocine 2b in the presence of excess sodium hydride. ms;(m/e) for the first component: 107(75%), 106(100%), 79(95%), 78(11%), 77(22%), 53(14%) and 41(22%).



29 2b 65

The fragmentation pathways of 65 are illustrated as shown in Scheme XIV.



Scheme XIV

Further work such as the preparative GC to isolate the first component is most desirable.

EXPERIMENTAL

Microanalyses were performed by the Australian Microanalytical Service, Melbourne, Australia. Melting points (mp) and boiling points (bp) are uncorrected. The following spectrometers were used: nuclear magnetic resonance (nmr), JEOL 60-HL (60 MHz) (in δ units, with TMS as internal standard unless stated otherwise); carbon nuclear magnetic resonance (^{13}C-nmr), JOEL FX-90Q (90 MHz) (in ppm, with TMS as internal standard unless stated otherwise); infrared (ir), Perkin-Elmer 283; mass spectrum (ms), VG 7070F high resolution mass spectrometer. Gas chromatographic analyses were performed on a Hewlett Packard 700 laboratory chromatograph equipped with silanized glass column packed with 3% OV-1 and on a Varian GC-3700 equipped with silanized glass column packed with 3% OV-17. Reagents and solvents were commerical grades and were purified by standard procedures.[24]

2-Cyclopentenone (44)

2-Cyclopentenone was prepared according to a modified procedure of Alder and Flock.[25] Freshly distilled

cyclopentadiene (123.5g, 1.87mol) was placed in a 250 ml three-necked flask and stirred vigorously and kept at a dry ice-acetone bath. Anhydrous hydrogen chloride (68.3 g, 1.87 mol) was bubbled into the neat liquid. Without further purification, the cyclopentenyl chloride was added dropwise to a solution of sodium dichromate dihydrate (155.3 g, 0.53 mol) in water (330 ml) in a 2-L flask that was immersed in an acetone-ice bath. The reaction mixture was stirred efficiently and kept at 0-10°C. Aqueous sulfuric acid (257 ml, 50% by volume) was then added slowly to the brownish mixture. The temperature of the reaction was maintained carefully below 10°C throughout the addition. The green mixture was diluted with water (400 ml) and extracted with chloroform (6 x 150 ml). Combined organic layers were washed with water (3 x 150 ml) followed by saturated sodium carbonate solution (3 x 150 ml) and dried over sodium sulfate. The solvent was then removed in vacuo. The residue was distilled through a short Vigreux column. Pure 2-cyclopentenone 44 (61.5 g, 40%) was obtained by fractional distillation under reduced pressure: bp 53-55°C/20 mm (lit[26]: bp 68-69°C/ 23 mm)

Bromoacetaldehyde Diethylacetal (66)

Bromoacetaldehyde diethylacetal was prepared according to known procedure.[27] Vinyl acetate (86 g, 1.00 mol) was transformed into 66 (118 g, 60%) and was freshly distilled before use: bp 76-78°C/25 mm (lit[27]: bp 64-65°C/16mm); nmr ($CDCl_3$) δ 4.6 (1H, t, H_1), 3.6 (4H, q, $-OCH_2$), 3.3 (2H, d, H_2) and 1.2 (6H, t, CH_3); ir (neat) 1150 and 1090 cm^{-1} (ketal).

Ketene Diethylacetal (1,1-diethoxyethene) (45)

Ketene diethylacetal was prepared according to the procedure given by McElvain and Kundiger.[28] Bromoacetaldehyde diethylacetal 66 (197 g, 1.00 mol) was transformed into 1,1-diethoxyethene 45 (75 g, 64.6%): bp 118-121°C/760 mm (lit[28]: bp 83-86°C/200mm).

6,6-Diethoxybicyclo[3.2.0]heptan-2-one (31)

A solution of cyclopentenone 44 (2.0 g, 24.4 mmol) and freshly distilled ketene diethylacetal 45 (20.0 g, 172 mmol) in pentane (400 ml) under nitrogen atmosphere was placed in a pyrex photochemical reactor and irradiated (400W, medium pressure mercury arc, Applied Photophysics 400LQ) at 0°C for 7.5 h. The pentane and excess ketene

diethylacetal were removed in vacuo. Distillation of the residue gave 6,6-diethoxybicyclo[3.2.0]heptan-2-one 31 (2.0 g, 41%): bp 58-60°C/0.1 mm; nmr ($CDCl_3$) δ 3.6-3.1 (4H, m, OCH_2), 3.0-1.8 (8H, m, H_1, H_3, H_4, H_5, H_7) and 1.3-1.0 (6H, m, CH_3); ir(neat) 1730 (carbonyl), 1145 and 1050 cm^{-1} (ketal).

6,6-Diethoxybicyclo[3.2.0]heptan-2-ol (47)

To a 250 ml two-necked round-bottomed flask fitted with a drying tube was placed a suspension of excess lithium aluminium hydride (1.8 g, 47.4 mmol) in dry tetrahydrofuran (75 ml). 6,6-diethoxybicyclo[3.2.0]heptan-2-one 31 (4.8 g, 24.4 mmol) in freshly distilled tetrahydrofuran (75 ml) was added dropwise at 0°C. After the addition was completed, the mixture was stirred for 4 h. Excess LAH was decomposed by the addition of ethyl acetate. The mixture was poured into ice-water (100 ml) and extracted with dichloromethane (4 x 100 ml). Combined organic extracts were washed with brine solution and dried over magnesium sulfate, filtered and evaporated in vacuo to give 6,6-diethoxybicyclo[3.2.0]-heptan-2-ol 47 in nearly quantitative yield, which was used in the next step without further purification: ir(neat) 3600-3200 (hydroxyl), 1150 and 1050 cm^{-1} (ketal).

2-endo-Hydroxybicyclo[3.2.0]heptan-6-one (32)

A mixture of 6,6-diethoxybicyclo[3.2.0]heptan-2-ol 47 (4.8 g, 24.0 mmol), dichloromethane (100 ml), water (10 ml) and 2 drops of concentrated hydrochloric acid was stirred for 4 h at room temperature. The mixture was then neutralized with 10% sodium hydroxide solution and was extracted with dichloromethane (2 x 50 ml). Combined organic extracts were washed with saturated sodium carbonate solution (50 ml), dried over magnesium sulfate, filtered and evaporated *in vacuo* to give crude 2-endo-hydroxybicyclo[3.2.0]heptan-6-one 32 which was purified by vacuum distillation (2.5 g, 85%): bp 72-73°C/0.10 mm; nmr ($CDCl_3$) δ 4.7-4.3 (1H, m, H_2), 3.8 (1H, bs, OH), 3.6-3.4 (1H, m, H_5), 3.1-2.9 (3H, m, H_1 and H_7) and 2.0-1.4 (4H, m, H_3 and H_4); ir(neat) 3600-3200 (hydroxyl), 1780 (carbonyl) and 1070 cm^{-1} (C-O).

Mesitylene sulfonyl chloride (67)

Mesitylene sulfonyl chloride 67 was synthesized according to the procedure of Wang and Cohen.[29] Mesitylene sulfonyl chloride (115.5 g, 66%) was obtained from freshly distilled mesitylene (150 g, 1.25 mol): mp 55-56°C (lit[29]: 57°C) which was recrystallized in pet. ether (60-80°C) before use.

thyl acetimidate hydrochloride (68)

Ethyl acetimidate hydrochloride 68 was synthesized ccording to the procedure given by Sandler and Karo.[30] cetonitrile (123 g, 3.00 mol), absolute ethanol (138 g, .00 mol) and dry hydrogen chloride (109.5 g, 3.00 mol) ere reacted to from ethyl acetimidate hydrochloride 68 325 g, 80%).

thyl acetohydroxamate (69)

Ethyl acetohydroxamate 69 was synthesized from 68 in wo steps by the procedure given by E. Schmidt.[31] Ethyl cetimidate hydrochloride (30 g, 0.24 mol) was allowed o react with K_2CO_3 (69.0 g, 0.5 mol) and then with ydroxylamine hydrochloride (21.3 g, 0.30 mol) to give thyl acetohydroxamate 69 (10 g, 40%): bp 72-74°C/18 mm (lit[31]: 59-60°C/13 mm); nmr ($CDCl_3$) δ 8.8-8.5 (C=N-OH, bs), 4.1-3.7 (2H, q, $-OCH_2$), 1.9 (3H, s, CH_3) and 1.4-1.1 (3H, t, $-OCH_2CH_3$).

O-Mesitylenesulfonylhydroxylamine (70)

O-Mesitylenesulfonylhydroxylamine 70 was synthesized in two steps from ethyl acetohydroxamate 69 and mesitylene

sulfonyl chloride 67. O-Mesitylenesulfonylhydroxylamine 70 (15 g, 50%) was obtained from ethyl acetohydroxamate 69 (7.0 g, 0.07 mol) and mesitylenesulfonyl chloride 67 (14.8 g, 70 mmol): mp 51-52°C (lit[32]: 54-55°C); nmr ($CDCl_3$) δ 7.0 (2H, m, H_3 and H_5), 5.6-5.3 (2H, bs, NH_2), 2.5 (6H, s, ortho-CH_3) and 2.3 (3H, s, para-CH_3).

4-endo-Hydroxy-2-oxo-octahydrocyclopenta[b]pyrrole (33a) and 4-endo-Hydroxy-1-oxo-octahydrocyclopenta[c]pyrrole (33b)

To a stirred solution of 2-endo-hydroxybicyclo[3.2.0]-heptan-6-one 32 (2.0 g, 15.9 mmol) in dichloromethane (20 ml) was added a solution of O-mesitylenesulfonyl-hydroxylamine 70 (4.0 g, 18.6 mmol) in dichloromethane (20 ml) at ice-acetone bath (-10°C). The reaction mixture was allowed to stand for ½ h. The solvent was removed *in vacuo* at room temperature to yield the crystalline oxime mesitylenesulfonate, which was then dissolved in benzene: methanol (3:1, 20 ml) and added dropwise to a stirred suspension of basic alumina (Merck, activity I, 100 g) in anhydrous methanol (100 ml). The mixture was stirred overnight and filtered by suction. The basic alumina was washed with anhydrous methanol (2 x 150 ml). The combined methanolic solution was concentrated *in vacuo* and the residue was chromatographed on silica gel (70-230 mesh) using

chloroform as eluent. The first component was methyl mesitylenesulfonate. Hydroxy-lactams 33a and 33b were eluted by acetone:chloroform (2:1). The eluate was concentrated in vacuo, which gave a white solid on refrigeration (1.7 g, 78%). Analysis by ^{13}C-nmr showed the ratio of 33a to 33b was about 3:1. 33a was isolated as white needles by successive recrystallization from ethyl acetate and then from methanol: mp 160-162°C; nmr (CD_3OD) δ for 33a 7.7-7.3 (1H, bs, NH), 4.3-3.8 (3H, m, H_4, H_{6a} and OH), 3.5-2.4 (2H, m, H_3), 2.5-2.1 (1H, m, H_{3a}) and 1.8-1.3 (4H, m, H_5 and H_6); ^{13}C-nmr (CD_3OD) for 33a 180.8 (C-2), 73.8 (C-4), 59.8 (C-6a), 42.3 (C-3a), 33.9 (C-3), 31.2 (C-5) and 30.9 (C-6); ir (KBr, disc) 3600-3100 (OH and NH) and 1685 cm^{-1} (C=O).

2-endo-Methanesulfonyloxybicyclo[3.2.0]heptan-6-one (51)

To a solution of dry pyridine (4.1 g, 51.6 mmol) in dry ether (9 ml) was added dropwise a solution of methanesulfonyl chloride (5.9 g, 51.6 mmol). The mixture was stirred at 0°C for 1 h. 2-endo-Hydroxybicyclo[3.2.0]-heptan-6-one 32 (1.2 g, 9.6mmol) was added dropwise and the mixture was stirred overnight. The solution was poured into dilute hydrochloric acid (40 ml, 10%) and was extracted with dichloromethane (3 x 150 ml). The combined organic solution was washed with dilute hydrochloric acid solution

(3 x 30 ml), dilute sodium hydroxide solution (3 x 30 ml) and dried over magnesium sulfate, filtered and evaporated *in vacuo* to give 2-*endo*-methanesulfonyloxybicyclo[3.2.0]-heptan-6-one 51 (1.5 g, 78%) which was purified by chromatography on silica gel (70-230 mesh) using benzene as eluent: nmr ($CDCl_3$) δ 5.2-4.9 (1H, m, H_2), 3.6-3.3 (1H, m, H_5), 3.1 (3H, s, CH_3), 3.0 (2H, m, H_7), 2.8 (1H, m, H_1) and 2.3-1.6 (4H, m, H_3 and H_4); ir(neat) 1780 (C=O), 1350 and 1170 cm^{-1} (CH_3SO_2O).

Reaction of 51 with O-mesitylenesulfonylhydroxylamine 70

2-Methanesulfonyloxybicyclo[3.2.0]heptan-6-one 51 (1.0 g, 5.0 mmol) in dichloromethane (4 ml) was added into a dichloromethane solution (4 ml) of MSH (1.2g, 5.6 mmol) at -10°C. The mixture was stirred for ½ h and the solvent was removed *in vacuo*, the residue was redissolved in benzene (30 ml) and added dropwise to a suspension of basic alumina in anhydrous methanol (200 ml) and stirred for 8 h. The solution was filtered by suction and the alumina was washed with anhydrous methanol (2 x 100 ml). Combined organic layers were removed *in vacuo* to give a viscous oil, which was chromatographed on silica gel (70-230 mesh) using chloroform as eluent. The first

component was methyl mesitylenesulfonate. Hydroxy-lactams 33a and 33b (0.5g, 75%) were obtained when eluted by acetone-chloroform (2:1) mixture.

4-endo-Methanesulfonyloxy-2-oxo-octahydrocyclopenta[b]pyrrole (34)

Method 1. From hydroxylamine-O-sulfonic acid

To a stirred solution of 2-methanesulfonyloxybicyclo[3.2.0]-heptan-6-one 51 (1.0 g, 5 mmol) and 95-97% formic acid (5 ml) was added dropwise the solution of hydroxylamine-O-sulfonic acid (15 mmol) in 95-97% formic acid (5 ml) at room temperature over a period of 5 min. The reaction mixture was then heated at about 60°C for 5 h. After cooling, the solution was poured into ice/water, neutralized with 10% sodium hydroxide solution, and then extracted with chloroform (2 x 30 ml). The combined organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The residue was chromatographed on silica gel (70-230 mesh) using acetone-chloroform (1:1) as eluant to give 4-methanesulfonyloxy-2-oxo-octahydrocyclo-penta[b]pyrrole 34 (0.2 g, 20%): mp 96-97°C; nmr ($CDCl_3$) δ 7.3-6.9 (1H, bs, NH), 5.1-4.9 (1H, m, H_4), 4.2-4.0 (1H, m, H_{6a}), 3.5-3.2 (1H, m, H_{3a}), 3.1 (3H, s, CH_3), 2.5-2.2 (2H, m, H_3) and 2.1-1.6 (4H, m, H_5 and H_6); ir (KBr, disc) 3600-3200 (NH), 1680 (C=O) and 1360 and 1180 cm^{-1} (CH_3SO_2O).

Method 2. From 4-endo-Hydroxy-2-oxo-octahydrocyclopenta[b]-pyrrole (33a)

4-endo-Hydroxy-2-oxo-octahydrocyclopenta[b]pyrrole 33a (150 mg, 1.07 mmol) was dissolved in dry tetrahydrofuran (25 ml) and was added dropwise into a suspension of sodium hydride (31.2 mg, 1.3 mmol) in dry tetrahydrofuran (5 ml) under nitrogen atmosphere. The solution was stirred at room temperature for 10 h until the hydrogen evolution subsided. Methanesulfonyl chloride (300 mg, 2.62 mmol) was added dropwise to the above mixture and was stirred for another 8 h at room temperature. The solution was then poured into a chloroform and tetrahydrofuran mixture (2:1, 60 ml), boiled and filtered when the solution was still hot. Evaporation of the filtrate in vacuo gave a yellowish oil which was chromatographed on silica gel (70-230 mesh) using acetone:chloroform (1:1) as eluant. The first fraction eluted was methanesulfonyl chloride. The desired lactam-methanesulfonate was eluted as the second fraction (140 mg, 60%). Unreacted hydroxylactam was isolated by flushing the column with acetone. 4-endo-Methanesulfonyloxy-2-oxo-octahydrocyclopenta[b]pyrrole 34 slowly crystallized on standing at room temperature: mp 96-97°C; nmr ($CDCl_3$) δ 7.7-7.2 (1H, bs, NH), 5.3-4.9 (1H, m, H_4), 4.3-4.0 (1H, m, H_{6a}), 3.6-3.3 (1H, m, H_{3a}), 3.1 (3H, s, CH_3), 2.6-2.4 (2H, m, H_3)

and 2.2-1.7 (4H, m, H_5 and H_6); ^{13}C-nmr ($CDCl_3$) δ 177.5 (C-2), 80.9 (C-4), 57.0 (C-6a), 40.9 (C-3a), 38.4 (CH_3), 30.5, 30.1 and 29.9 (C-3, C-5 and C-6); ir (KBr, disc) 3600-3200 (NH), 1680 (C=O), 1360 and 1180 cm^{-1} (CH_3SO_2O); ms m/e 219 (5%), 141 (1%), 140 (13%), 124 (24%), 123 (100%) 113 (1%), 112 (12%), 84 (13%), 83 (10%), 79 (22%), 67 (28%) and 66 (10%).

4-endo-p-Toluenesulfonyloxy-2-oxo-octahydrocyclopenta[b]-pyrrole (35)

4-endo-Hydroxy-2-oxo-octahydrocyclopenta[b]pyrrole 33a (100 mg, 0.71 mmol) was dissolved in dry tetrahydrofuran (20 ml) and was added dropwise into a suspension of sodium hydride (36 mg, 1.5 mmol) in dry tetrahydrofuran (5 ml) under nitrogen atmosphere. The solution was stirred at room temperature for 8 h until the hydrogen evolution subsided. p-Toluenesulfonyl chloride (572 mg, 3 mmol) in tetrahydrofuran (5 ml) was added dropwise to the above mixture and was stirred for another 8 h at room temperature. The solution was then poured into a chloroform:tetrahydrofuran mixture (2:1, 60 ml), boiled and filtered when the solution was still hot. Evaporation of the filtrate in vacuo gave a yellowish solid which was chromatographed on silica gel (70-230 mesh) using chloroform:acetone (1:1) as eluant. The first fraction

eluted was p-toluenesulfonyl chloride. The lactam-p-toluenesulfonate (120 mg, 62%) was eluted as the second fraction. Unreacted hydroxylactam was isolated by flusing the column with acetone. 4-endo-p-Toluenesulfonyloxy-2-oxo-octahydrocyclopenta[b]pyrrole 35 slowly solidified on refrigeration. An analytical sample of 35 was obtained by recrystallization from pet. ether (40-60°C) and dichloromethane as colorless crystals: mp 154-155°C; nmr ($CDCl_3$) δ 8.0-7.2 (5H, m, NH, ortho-H and meta-H), 5.1-4.7 (1H, m, H_4), 4.2-3.8 (1H, m, H_{6a}), 3.2-2.8 (1H, m, H_{3a}), 2.6 (3H, s, CH_3), 2.5-2.3 (2H, m, H_3) and 2.0-1.7 (4H, m, H_5 and H_6); ^{13}C-nmr ($CDCl_3$) δ 177.6 (C-2), 145.1, 133.7, 130.0 and 127.7 (benzene ring carbons), 81.6 (C-4), 57.1 (C-6a), 39.9 (C-3a), 30.4, 29.8 and 29.3 (C-3, C-5 and C-6) and 21.6 (CH_3); ir (KBr, disc) 3500-3200 (NH), 1698 (C=O), 1362 and 1183 cm^{-1} (p-CH_3-C_6H_4-SO_2O-); ms (m/e) 295 (29%), 155 (34%), 141 (2%), 140 (23%), 124 (79%), 123 (99%), 113 (1%), 112 (6%), 91 (100%), 84 (16%), 83 (5%) 67 (21%) and 66 (12%).

Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74; S, 10.86
Found: C, 56.97; H, 5.97; N, 4.52; S, 10.80

7,7-Dichlorobicyclo[3.2.0]hept-2-en-6-one (36)

To a vigorously stirred solution of freshly distilled cyclopentadiene (82 g, 1.24 mol) and dichloroacetyl chloride (91.9 g, 0.62 mol) in dry hexane (500 ml) was added dry triethylamine (65.4 g, 0.65 mol) in dry hexane (400 ml) over a period of 3 h at 0°C. After stirring for an additional 15 h at room temperature under an atmosphere of nitrogen, the reaction mixture was filtered and the residue was washed with hexane. The solvent was removed in vacuo, yielding a brownish liquid (92.1 g). Vacuum distillation afforded pure 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one 36 (89.0 g, 81%): bp 40-41°C/0.1 mm (lit[16]: 49-50°C/0.3 mm); nmr ($CDCl_3$) δ 6.1-5.7 (2H, m, CH=CH), 4.4-3.9 (2H, m, H_1 and H_5) and 2.7-2.5 (2H, m, H_4); ir(neat) 1805 (C=O).

Bicyclo[3.2.0]hept-2-en-6-one (37)

To a vigorously stirred suspension of zinc dust (22.0 g, 0.34 mol) in glacial acetic acid (40 ml) at room temperature was added dropwise of 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one 36 (10.0 g, 0.056 mol) in glacial acetic acid (10 ml). After addition was completed, the temperature was raised to and maintained at 70°C for 1 h. The reaction mixture was

cooled and treated with ether, and the zinc residue was filtered. The ethereal layer was washed with a saturated sodium carbonate solution to remove the acetic acid and dried over magnesium sulfate. The solvent was removed *in vacuo* at ca. 10°C and pure bicyclo[3.2.0]hept-2-en-6-one 37 (5.5 g, 90.9%) was isolated by vacuum distillation: bp 79-80°C/30 mm (lit[16]: 60°C/15 mm); nmr ($CDCl_3$) δ 5.9-5.6 (2H, m, CH=CH), 4.0-3.6 (2H, m, H_7), 3.6-3.0 (1H, m, H_5), 2.8-2.3 (3H, m, H_1 and H_4); ir (neat) 1776 cm^{-1} (C=O).

2-exo-3-endo-Dibromobicyclo[3.2.0]heptan-6-one (38)

Bromine (1.54g, 9.64 mmol) in carbon tetrachloride (4 ml) was added dropwise to a stirred solution of bicyclo[3.2.0]hept-2-en-6-one 37 (1.0 g, 9.26 mmol) in carbon tetrachloride (13 ml) containing sodium hydrogen carbonate (2.0 g, 23.8 mmol) at 0°C. Stirring was continued for 3 h at 0°C before the solution was stored in refrigerator for 16 h. The colorless solution was filtered and the filtrate was evaporated *in vacuo*. The residue was taken up in the minimum quantity of pet. ether (40-60°C) and crystallized on refrigeration to give 2-exo-3-endo-dibromobicyclo[3.2.0]heptan-6-one 38 (1.9 g, 76.4%): mp 57-58°C (lit[15]: 59-60°C); nmr ($CDCl_3$) δ 4.9-4.6 (2H, m, H_2 and H_3), 4.0-3.8 (1H, m, H_5), 3.6-3.2 (3H, m, H_7 and H_1) and 3.0-2.6 (2H, m, H_4); ir (KBr, disc) 1780 cm^{-1} (C=O).

2-exo-Bromo-3-endo-methoxybicyclo[3.2.0]heptan-6-one (39)

The bicyclo[3.2.0]hept-2-en-6-one 37 (5 g, 46.3 mmol) was dissolved in methanol (70 ml) and N-bromosuccinimide (NBS) (8.2 g, 46.3 mmol) was added with stirring. After stirring for 18 h at room temperature, the solution was diluted with ether (30 ml) and extracted with water (6 x 15 ml). The aqueous extracts were separately washed with ether (2 x 20 ml). The combined organic fractions were dried over magnesium sulfate and filtered. The solvent was removed in vacuo to give a brownish residue. Vacuum distillation gave pure 2-exo-bromo-3-endo-methoxybicyclo-[3.2.0]heptan-6-one 39 (8.6 g, 85%): bp 64-66°C/0.05 mm (lit[15]: 70°C (oven temperature)/0.005 mm); nmr ($CDCl_3$) δ 4.45 (1H, m, H_3), 4.3-4.0 (2H, m, H_2 and H_5), 3.5-3.4 (3H, m, H_7 and H_1), 3.1 (3H, s, CH_3) and 2.4-2.0 (2H, m, H_4); ir(neat) 1795 (C=O) and 1094 cm^{-1} (C-O).

4-exo-Brome-5-endo-methoxy-2-oxo-octahydrocyclopenta[b]-pyrrole (41a) and 4-exo-Bromo-5-endo-methoxy-2-oxo-octahydrocyclopenta[c]pyrrole (41b)

To a stirred solution of 2-exo-bromo-3-endo-methoxy-bicyclo[3.2.0]heptan-6-one 39 (2.0 g, 9.14 mmol) in dichloromethane (10 ml) was added dropwise a solution of MSH (2.6 g, 12.0 mmol) in dichloromethane (10 ml) at -10°C and the reaction mixture was allowed to stand for

15 min. The solvent was removed under reduced pressure to give crystalline oxime-sulfonate which was dissolved in benzene:methanol (3:1, 8 ml) and was added into a stirred slurry of basic alumina (80 g) in anhydrous methanol (150 ml). The mixture was stirred for 4 h and filtered by suction. The basic alumina was washed with anhydrous methanol (2 x 70 ml) and the combined methanolic solution was concentrated in vacuo. The residue was dissolved in chloroform (70 ml) and the insoluble material was removed by filtration. After evaporation of the solvent, the residue was chromatographed on silica gel (70-230 mesh) using chloroform as eluent. The first component was methyl mesitylenesulfonate. Products 41a and 41b (1.6 g, 74.8%) were eluted by acetone:chloroform (1:2) as inseparable isomeric mixture: nmr ($CDCl_3$) δ for 41a and 41b 8.0-7.7 (1H, bs, NH), 4.4-3.8 (3H, m, H_4, H_5 and H_{6a}), 3.4 (3H, s, CH_3), 3.2-3.0 (1H, m, H_{3a}), 2.8-1.8 (4H, m, H_3 and H_6); ^{13}C-nmr ($CDCl_3$) δ for 41a and 41b 179.7, 176.7, 88.9, 88.5, 77.3, 57.3, 57.1, 56.9, 56.3, 56.1, 47.5, 47.2, 46.3, 43.1, 36.5 and 31.4; ir (KBr, disc) 3500-3200 (NH), 1662 (C=O) and 1104 cm^{-1} (C-O).

3,3-Dichloro-2-oxo-hexahydrocyclopenta-4-en[b]pyrrole (42)

To a stirred solution of 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one 36 (3.0 g, 16.9 mmol) in dichloromethane (20 ml)

was added dropwise a solution of MSH (4.3 g, 20.0 mmol) in dichloromethane (20 ml) at room temperature. The reaction mixture was then stirred at room temperature for an additional 0.5 h and allowed to stand for 0.5 h. The solvent was removed in vacuo to yield a colorless oil which was then dissolved in benzene:methanol (3:1, 20 ml) and added dropwise to a stirred suspension of basic alumina (110 g) in anhydrous methanol (110 ml). The mixture was stirred for 4 h and filtered by suction. The basic alumina was washed with methanol (2 x 100 ml). The combined methanolic solution was concentrated in vacuo. The residue was dissolved in chloroform (30 ml) and the insoluble material was removed by filtration. After evaporation of the solvent, the residue was chromatographed on silica gel (70-230 mesh) using chloroform as eluent. The first fraction was a mixture of methyl mesitylenesulfonate and 7,7-dichlorobicyclo[3.2.0]-hept-2-en-6-one 36. The lactam product, 3,3-dichloro-2-oxo-hexahydrocyclopenta-4-en[b]pyrrole 42 was eluted by acetone:chloroform (1:2). The eluate was concentrated in vacuo to give a white solid (2.2 g, 68%). An analytical sample of 42 was obtained as colorless crystals by recrystallization from pet. ether (40-60°C) and dichloromethane: mp 138-140°C; nmr ($CDCl_3$) δ 8.5-8.0 (1H, bs, NH), 6.0-5.7 (2h, m, H_4 and H_5), 4.6-4.4 (1H, m, H_{3a}), 4.3-4.1 (1H, m, H_{6a}) and 2.8-2.5 (2H, m, H_6); ^{13}C-nmr ($CDCl_3$) δ 168.9 (C-2),

131.9, 128.2 (C-4 and C-5), 84.1 (C-3), 63.4 (C-3a), 54.3 (C-6a) and 39.4 (C-6); ir (KBr, disc) 3500-3200 (NH) and 1726 cm^{-1} (C=O); ms (m/e) 195 (5.3%), 193 (34%), 191 (52%), 158 (25%), 156 (75%), 152 (2%), 151 (2%), 130 (3%), 113 (100%), 66 (9%) and 65 (25%).

Anal. Calcd for $C_7H_7Cl_2NO$: C, 43.77; H, 3.67; Cl, 36.92
Found: C, 43.83; H, 3.87; Cl, 37.30

2-oxo-Hexahydrocyclopenta-4-en[b]pyrrole (43)

To a vigorously stirred suspension of zinc dust (0.4 g, 6.1 mmol) in glacial acetic acid (2 ml) at room temperature was added dropwise a solution of 3,3-dichloro-2-oxo-hexahydrocyclopenta-4-en [b]pyrrole 42 (2.0 g, 10.4 mmol) in glacial acetic acid (4 ml). After addition was completed, the temperature was raised and maintained at 70°C for 20 min. The reaction mixture was cooled and treated with chloroform, and the zinc residue was filtered. The organic layer was washed with a saturated sodium carbonate solution to remove the acetic acid and dried over magnesium sulfate and filtered. The solvent was removed in vacuo to give a white solid (1.1 g, 89%). An analytical sample of 2-oxo-hexahydrocyclopenta-4-en[b]pyrrole 43 was obtained as colorless needles by recrystallization from pet. ether (40-60°C) and dichloromethane: mp 114-116°C; nmr ($CDCl_3$)

δ 8.0-7.5 (1H, bs, NH), 5.9-5.6 (2H, m, H_4 and H_5), 4.5-4.3 (1H, m, H_{6a}), 3.6-3.4 (1H, m, H_{3a}), 2.7-2.2 (4H, m, H_3 and H_6); ^{13}C-nmr ($CDCl_3$) δ 178.2 (C-2), 131.7, 128.7 (C-4 and C-5), 56.4 (C-6a), 46.1 (C-3), 35.8 (C-3a) and 34.9 (C-6); ir (KBr, disc) 3500-3200 (NH) and 1683 cm^{-1} (C=O); ms (m/e) 123 (100%), 122 (3%), 80 (53%), 79 (27%) and 66 (1%).

Anal. Calcd for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37
Found: C, 68.53; H, 7.32; N, 11.46

4-exo-5-endo-Dibromo-2-oxo-octahydrocyclopenta[b]pyrrole (40a)

Method 1. From 2-exo-3-endo-dibromobicyclo[3.2.0]heptan-6-one 38

To a stirred solution of 2-exo-3-endo-dibromobicyclo-[3.2.0]heptan-6-one 38 (3.0 g, 11.2 mmol) in dichloromethane (20 ml) was added a solution of MSH (3.2 g, 15 mmol) in dichloromethane (20 ml) at -10°C. The reaction mixture was allowed to stand for 0.5 h. The solvent was removed in vacuo at room temperature to yield the crystalline oxime mesitylene-sulfonate which was dissolved in benzene:methanol (3:1, 20 ml) and added dropwise to a stirred suspension of basic alumina (100 g) in anhydrous methanol (100 ml). The mixture was stirred for 4 h and filtered by suction. The basic alumina was washed with methanol (2 x 100 ml). The combined methanolic

solution was concentrated *in vacuo*. The residue was dissolved in chloroform (80 ml) and the insoluble material was removed by filtration. After evaporation of the solvent, the residue was chromatographed on silica gel (70-230 mesh) using chloroform as eluent. The first component was methyl mesitylenesulfonate. The lactam-dibromide, 4-*exo*-5-*endo*-dibromo-2-oxo-octahydrocyclopenta[c]pyrrole 40b (0.6 g, 18.9%) was eluted with acetone:chloroform (1:2). The desired isomer, 4-*exo*-5-*endo*-dibromo-2-oxo-octahydrocyclopenta[b]pyrrole 40a (1.6 g, 52.1%) was obtained from further flushing the column. Compound 40a was obtained as colorless crystals when recrystallized from benzene: mp 150-152°C; nmr (DMSO) δ 8.0-7.7 (1H, bs, NH), 4.8-4.2 (3H, m, H_4, H_5 and H_{6a}), 3.3-3.2 (1H, m, H_{3a}) and 2.6-2.2 (4H, m, H_3 and H_5); ir (KBr, disc) 3500-3150 (NH) and 1684 cm^{-1} (C=O).

Method 2. From 2-oxo-hexahydrocyclopenta-4-en[b]pyrrole (43)

To a solution containing 2-oxo-hexahydrocyclopenta-4-en[b]pyrrole 43 (1.0 g, 8.13 mmol) in dichloromethane (60 ml) was added dropwise a solution of bromine (4.3 g, 26.4 mmol) in dichloromethane (60 ml) over 1 h. The resulting red solution was stirred overnight at room temperature and poured into water (300 ml). The aqueous layer was discarded and the

organic layer was washed with saturated sodium hydrogen carbonate solution (100 ml) and then water (100 ml) and dried over magnesium sulfate. Evaporation of the solvent *in vacuo* gave a yellow solid which was chromatographed on silica gel (70-230 mesh) using acetone:chloroform (1:1) as eluant. The eluate was concentrated *in vacuo* to give a white solid (1.4 g, 61%) which upon recrystallization from benzene gave 4-*exo*-5-*endo*-dibromo-2-oxo-octahydrocyclopenta[b]pyrrole 40a as colorless crystals: mp 150-151°C; nmr (DMSO) δ 8.0-7.7 (1H, bs, NH), 4.7-4.2 (3H, m, H_4, H_5, H_{6a}), 3.3-3.2 (1H, m, H_{3a}) and 2.6-2.2 (4H, m, H_3 and H_6); ^{13}C-nmr (DMSO) δ 176.3 (C-2), 59.8 (C-6a), 48.3, 46.0 (C-4 and C-5),43.9 (C-3a), 37.1 and 36.7 (C-3 and C-6); ir (KBr, disc) 3500-3200 (NH) and 1683 cm^{-1} (C=O); ms (m/e) 281 (not observed), 204 (82%), 202 (100%), 123 (27%), 122 (13%), 84 (3%), 83 (16%), 80 (33%) and 79 (41%).

Anal. Calcd for $C_7H_9Br_2NO$: C, 29.72; H, 3.21; N, 4.95; Br, 56.48
Found: C, 29.90; H, 3.31; N, 4.91; Br, 55.90

4-*exo*-Bromo-5-*endo*-methoxy-2-oxo-octahydrocyclopenta[b]pyrrole (41a

2-oxo-Hexahydrocyclopenta-4-en[b]pyrrole 43 (1.5 g, 12.2 mmol) was dissolved in dry methanol (30 ml) and NBS (2.2 g, 12.5 mmol) was added with stirring. After 18 h at room temperature, the solution was diluted with chloroform (30 ml) and extracted

with water (6 x 15 ml). The aqueous extracts were washed with chloroform (2 x 20 ml). The combined organic layers were dried over magnesium sulfate and filtered. The solvent was removed in vacuo to give a white solid (2.4 g, 84%) which on crystallization from benzene gave 4-exo-bromo-5-endo-methoxy-2-oxo-octahydrocyclopenta[b]pyrrole 41a as colorless crystals: mp 127-128°C; nmr ($CDCl_3$) δ 8.0-7.7 (1H, bs, NH), 4.5-3.9 (3H, m, H_4, H_5 and H_{6a}), 3.4 (3H, s, CH_3), 3.3-3.1 (1H, m, H_{3a}) and 2.7-2.3 (4H, m, H_3 and H_6); ^{13}C-nmr ($CDCl_3$) δ 176.7 (C-2), 88.5 (C-5), 77.1 (CH_3), 57.1 (C-6a), 47.2 (C-4), 43.1 (C-3a) and 36.5 , 31.4 (C-6 and C-3); ir (KBr, disc) 3500-3200 (NH), 1680 (C=O) and 1104 cm^{-1} (C-O); ms (m/e) 233 (not observed), 154 (82%), 123 (4%), 122 (19%), 96 (100%), 84 (5%), 83 (5%), 80 (13%) and 79 (18%).

Anal. Calcd for $C_8H_{12}BrNO_2$: C, 41.05; H, 5.17; N, 5.98
Found: C, 41.13; H, 5.23; N, 5.76

Boron tetrahydrofuranate (71)

The complex was prepared by a modification of known procedure.[19] To a stirred suspension of sodium borohydride

(4.1 g, 0.11 mol) in dry tetrahydrofuran (150 ml) was added dropwise a solution of distilled boron trifluoride etherate (21.4 g, 0.15 mol) in dry tetrahydrofuran (30 ml). The solution was stirred at room temperature for 10 h under nitrogen atmosphere. Under a nitrogen atmosphere, the solid sodium tetrafluoroborate was filtered, the filtrate (110 ml) has a concentration of approximately 1.1M in borane (0.12 mol, 81%), as determined by measuring the hydrogen evolved on hydrolysis, which was stored under nitrogen in a refrigerator.

4-endo-Methanesulfonyloxy-octahydrocyclopenta[b]pyrrole (27)

4-Methanesulfonyloxy-2-oxo-octahydrocyclopenta[b]pyrrole 34 (50 mg, 0.23 mol) was mixed with borane tetrahydrofuranate (10 ml, 1.1M, 11.3 mmol) and reflux under nitrogen for 3 h. The reaction mixture was set aside at room temperature for 1 h. Concentrated hydrochloric acid(5 ml, 36%) was carefully added and the mixture was stirred for 2 h. It was poured into chloroform (40 ml) and solid potassium hydroxide was added to adjust the pH to alkaline. The aqueous layer was extracted with chloroform (2 x 20 ml). The combined organic layers were washed with brine solution (20 ml) and dried over magnesium sulfate, filtered and evaporated in vacuo to give a colorless liquid, which was a mixture of the desired product 27 and significant amount of 1,4-butanediol formed from the decomposition of tetrahydrofuran

during work up. 1,4-butanediol was removed by high vacuum distillation, the residue being crude. Crude 27 was dissolved in 10% hydrochloric acid solution (20 ml). The solution was filtered, neutralized carefully with solid sodium hydroxide until the pH became 10, and extracted with chloroform (3 x 30 ml). The combined organic layers were washed with brine solution (20 ml) and dried over magnesium sulfate, filtered and evaporated in vacuo to give 4-endo-methanesulfonyloxy-octahydrocyclopenta[b]pyrrole 27 (28.3 mg, 60%). Attempts to further purify it by chromatography led to decomposition: nmr ($CDCl_3$) δ 5.0-4.6 (1H, m, H_4), 3.8-3.0 (2H, m, H_{3a} and H_{6a}), 3.1 (3H, s, CH_3), 2.9-2.7 (2H, m, H_2) and 2.0-1.4 (7H, m, H_3, H_5, H_6 and NH); ir (neat) 3600-3200 (NH), 1360 and 1180 cm^{-1} (CH_3SO_2O); ms (m/e) 205 (not observed), 110 (100%), 109 (25%), 108 (31%), 107 (3%), 106 (4%), 82 (16%), 81 (40%), 80 (37%), 79 (18%), 68 (72%) and 67 (47%); ms (exact mass for m/e 110) $C_7H_{12}N$ found 110.0961 (calcd 110.0969)

4-endo-p-toluenesulfonyloxy-octahydrocyclopenta[b]pyrrole 28

The procedure was the same as described in the reaction of 27 with 71. 4-endo-p-Toluenesulfonyl-2-oxo-octahydrocyclopenta[b]pyrrole 35 (0.1g, 0.34 mmol) was transformed into 4-endo-p-toluenesulfonyloxy-octahydrocyclopenta[b]pyrrole 28 (62 mg, 65%): nmr ($CDCl_3$) δ 8.1-7.3 (4H, m, ortho-H and meta-H), 5.0-4.7 (1H, m, H_4), 3.8-3.4 (2H, m, H_{3a} and H_{6a}), 3.0-

2.7 (2H, m, H_2), 2.5 (3H, s, CH_3), 2.0-1.4 (7H, H_3, H_5, H_6 and NH); ir(neat) 3600-3200 (NH), 1359 and 1191 cm^{-1} (CH_3-C_6H_4-SO O); ms (m/e) 281 (not observed), 110 (100%), 109 (14%), 108 (17%), 91 (93%), 80 (39%), 79 (17%), 68 (65%) and 67 (23%); ms (exact mass for m/e 110) $C_7H_{12}N$, found 110.0963 (calcd 110.0969).

4-exo-5-endo-Dibromooctahydrocyclopenta[b]pyrrole (29)

The procedure was the same as described in the reaction of 27 with 71. 4-exo-5-endo-Dibromo-2-oxo-octahydrocyclopenta[b]pyrrole 40a (1.0 g, 3.6 mmol) was transformed into 4-exo-5-endo-dibromooctahydrocyclopenta[b]pyrrole 29 (0.6 g, 62%):nmr ($CDCl_3$) δ 4.6-3.3 (4H, m, H_4, H_5, H_{6a} and H_{3a}), 3.0-2.6 (2H, m, H_2), 2.4-2.2 (2H, m, H_6) and 2.0-1.6 (3H, m, H_3 and NH); ir(neat) 3500-3200 cm^{-1} (NH); ms (m/e) 267 (not observed), 190 (100%), 188 (100%), 109 (36%), 108 (31%), 80 (17%), 79 (13%), 69 (64%); ms (exact mass for m/e 188) $C_7H_{11}BrN$, found 188.0050 (calcd 188.0050).

4-exo-Bromo-5-endo-methoxyoctahydrocyclopenta[b]pyrrole (30)

The procedure was the same as described in the reaction of 27 with 71. 4-exo-Bromo-5-endo-methoxy-2-oxo-octahydrocyclopenta[b]pyrrole 41a (1 g, 4.3 mmol) was transformed

into 4-exo-bromo-5-endo-methoxyoctahydrocyclopenta[b]pyrrole 30 (0.6 g, 65%): nmr ($CDCl_3$) δ 4.2-3.6 (3H, m, H_4, H_5 and H_{6a}), 3.45 (3H, s, CH_3), 3.3-3.1 (1H, m, H_{3a}), 3.0-2.2 (4H, m, H_2 and H_5) and 2.0-1.4 (3H, m, H_3 and NH); ir(neat) 3600-3200 (NH) and 1092 cm^{-1}(C-O); ms (m/e) 219 (not observed), 140 (100%), 109 (9%), 108 (16%), 80 (13%), 79 (10%), 69 (17%) and 68 (25%); ms (exact mass for m/e 140) $C_8H_{14}NO$, found 140.1061 (calcd 140.1075).

Reaction of 4-endo-p-toluenesulfonyloxy-octahydrocyclopenta[b]-pyrrole 28 with potassium tetrachloroplatinate (II)

A mixture of 4-endo-p-toluenesulfonyloxy-octahydro-cyclopenta[b]pyrrole 28 (30 mg, 0.11 mmol), potassium tetrachloroplatinate (II) (45.7 mg, 0.11 mmol), and sodium carbonate crystal (85.8 mg, 0.3 mmol) in 80% ethanol (10 ml) was refluxed under nitrogen atmosphere for 10 h. After cooling, the solution was filtered and the filtrate was extracted with chloroform (3 x 10 ml). The combined organic layers were washed with brine solution and dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo to yield a light-brown oil. The nmr spectrum of this oil showed an absorption pattern at δ 7.9-7.1 and complex absorption patterns from δ 4.0-0.6. The structure of this oil was yet unidentified.

Reaction of 28 with sodium hydride in tetrahydrofuran.

A mixture of 4-endo-p-toluenesulfonyloxy-octahydrocyclopenta[b]pyrrole 28 (20 mg, 0.07 mmol) in dry tetrahydrofuran (6 ml) was refluxed for 8 h under nitrogen atmosphere. The resulting solution was stirred at room temperature for 6 h. The solution was filtered and the residue was washed with chloroform (3 x 10 ml). The organic layer was evaporated in vacuo to give a yellowish oil which was shown to be the starting material by the proton nmr spectrum.

Solvolytic study of 29 in absolute ethanol

A mixture of 4-exo-5-endo-dibromooctahydrocyclopenta[b]-pyrrole 29 (0.1 g, 0.37 mmol) and 2,2,6,6-tetramethyl-4-piperidinol (58.2 mg, 0.37 mmol) in 98% ethanol (10 ml) was refluxed under nitrogen atmosphere for 24 h. The solution was evaporated in vacuo to afford a brownish oil. Acetone (5 ml) was added to precipitate the 2,2,6,6-tetramethyl-4-piperidinol and the solution was filtered. The filtrate was concentrated in vacuo to yield a brownish oil which was the starting material as suggested by its proton nmr spectrum.

Solvolytic study of 29 in 80% ethanol

The procedure was the same as described in the reaction

of 29 in absolute ethanol. 4-exo-5-endo-dibromooctahydrocyclopenta[b]pyrrole 29 (100 mg, 0.37 mmol) gave also a brownish oil which was shown to be the starting material by its proton nmr spectrum.

Solvolytic study of 30

(A) in absolute ethanol.

A mixture of 4-exo-bromo-5-endo-methoxyoctahydrocyclopenta[b]pyrrole 30 (100 mg, 0.46 mmol) and 2,2,6,6-tetramethyl-4-piperidinol (72.3 mg, 0.46 mmol) in absolute ethanol (15 ml) was refluxed under nitrogen atmosphere for 24 h. Unreacting starting material was obtained quantitatively after work up.

(B) in 80% ethanol

A mixture of 4-exo-bromo-5-endo-methoxyoctahydrocyclopenta[b]pyrrole 30 (100 mg, 0.46 mmol) and 2,2,6,6-tetramethyl-4-piperidinol (72.3 mg, 0.46 mmol) in 80% ethanol (15 ml) was refluxed under nitrogen atmosphere for 24 h. After work up, unreacted starting material was obtained.

Reaction of 29 with sodium hydride in tetrahydrofuran

A mixture of 4-exo-5-endo-dibromooctahydrocyclopenta[b]-pyrrole 29 (200 mg, 0.75 mmol) and sodium hydride (48 mg, 2.0 mmol) in dry tetrahydrofuran (20 ml) was refluxed for 36 h under nitrogen atmosphere. The resulting solution was then stirred at room temperature for 8 h. The solution was filtered and the residue was washed with chloroform (3 x 10 ml). The organic layer was evaporated in vacuo to give a viscous brown oil: nmr ($CDCl_3$) δ 8.5-8.3, 6.2-5.5 and complex absorption patterns from 5.0-1.1. GC-MS revealed 2 components in the crude product. Ms (m/e) for the first component (retention time 5.5 min) 107 (75%), 106 (100%), 80 (53%), 79 (95%), 78 (11%), 77 (22%), 53 (14%) and 41 (22%). Ms (m/e) for the second component (retention time 7.8 min) 207 (13%), 85 (16%), 83 (24%), 71 (100%), 69 (10%) and 43 (49%).

Reaction of 30 with sodium hydride in tetrahydrofuran

The procedure was the same as described in the reaction of 29 with sodium hydride above. 4-exo-Bromo-5-endo-methoxy-octahydrocyclopenta[b]pyrrole (200 mg, 0.91 mmol) was transformed to a brown oil: nmr ($CDCl_3$) δ 8.5-8.3, 6.2-5.6, 5.0-3.6, 3.4 and 3.0-1.0; GC-MS revealed 3 components in the crude product. Ms (m/e) for the first component (retention

time 10 min) 281 (11%), 237 (17%), 207 (100%), 193 (20%), 108 (33%), 96 (14%), 94 (15%), 83 (11%), 80 (14%), 79 (19%) and 71 (31%); ms (m/e) for the second component (retention time 13 min) 139 (36%), 138 (14%), 124 (38%), 108 (100%), 107 (29%), 106 (43%), 79 (58%), 77 (27%), 59 (41%), 55 (21%), 53 (19%) and 41 (51%); ms (m/e) for the third component (retention time 14.5 min) 163 (31%), 161 (12%), 146 (16%), 145 (28%), 133 (100%), 131 (39%), 123 (11%), 119 (48%), 103 (68%), 89 (38%), 77 (25%), 75 (32%), 72 (33%), 59 (33%) and 55 (30%).

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